REPORT OF
THE GLAUCOMA PANEL

Volume Two / Part Four

# vision research

## A NATIONAL PLAN

1983-1987

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1983
vol 2
part 4

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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# PREFACE

*THIS IS THE Report of the Glaucoma Panel*, which is Part Four of *Volume Two, Reports of the Program Panels*, of the multivolume report of the National Advisory Eye Council entitled, *Vision Research—A National Plan: 1983–1987.*

The complete National Plan presents a comprehensive and detailed assessment of the current National Eye Institute program as well as specific recommendations for program development over the next five years. These include program priorities and projections of resource requirements for each major area of vision research that the NEI supports. Readers desiring additional information should consult the following volumes:

*Executive Summary* (Overview of the entire Plan).
*Volume One—The 1983 Report of the National Advisory Eye Council* (Background, Summary Panel Reports and Resource Requirements, Implementation Strategy, Cross-Cutting Research Areas and Issues, Planning Participants, Planning Strategy and Process).

*Volume Two—Reports of the Program Panels*

- **Part One**—*Report of the Retinal and Choroidal Diseases Panel*
- **Part Two**—*Report of the Corneal Diseases Panel*
- **Part Three**—*Report of the Cataract Panel*
- **Part Four**—*Report of the Glaucoma Panel*
- **Part Five**—*Report of the Strabismus, Amblyopia, and Visual Processing Panel*
- **Part Six**—*Report of the Panel on Visual Impairment and Its Rehabilitation.*

*Volume Three—Support for Vision Research* (Data on vision research projects supported by the NEI in FY 1981 and by other government and private organizations in FY 1980).

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# SUMMARY

## INTRODUCTION

*IN GLAUCOMA*, visual function is lost due to irreversible damage to the optic nerve. There are several types of glaucoma, typically characterized by elevated intraocular pressure, and it is this rise in pressure that is causally related to their common pathological outcome. If glaucoma is detected early and treated promptly, the progression of the disease can often be stopped or slowed by treatment to reduce the intraocular pressure, and loss of vision or blindness can be prevented.

An estimated 62,000 people in the United States were blind from glaucoma in 1978, making this disease the leading cause of blindness in this country. About 2 million Americans are known to have glaucoma, but surveys suggest that perhaps a million additional people may have some signs of the disease which can be detected by an ophthalmologist, yet are unaware of their condition. A much larger group, estimated to number as many as 5 to 10 million, has ocular hypertension, a condition characterized by elevated intraocular pressure but with no evidence of optic nerve damage. Some of these people ultimately will develop the optic nerve damage and visual loss typical of glaucoma. A significant number of people with "normal" intraocular pressure also have the optic nerve damage and visual loss typical of glaucoma, a condition defined as "low tension glaucoma." Glaucoma is a disease predominantly associated with aging, although it may occur at any time in life. An estimated 722,000 persons aged 65 and over—3 out of every 100—have the disease.

Intraocular pressure is maintained at a given level by a balancing of the rate at which aqueous humor is produced by the ciliary body and the rate at which it leaves the eye from the anterior chamber through outflow channels.

In the major outflow pathway, aqueous humor filters through the trabecular meshwork—which is in the "angle" of the eye where the iris and cornea are joined—filters into the canal of Schlemm drains into collector vessels, and finally enters the venous circulation. In almost all cases of glaucoma, intraocular pressure rises because of an obstruction to fluid outflow, mainly in the trabecular meshwork (Figure).

Glaucoma is discovered primarily by detection of increased pressure; the diagnosis is then confirmed by measurement of changes in the visual field and the ophthalmoscopic appearance of the optic nerve head. Aqueous humor production may be diminished by drug or surgical treatments, and aqueous humor outflow may be improved by drug treatment or, failing that, by laser treatment to improve outflow or fistulizing surgery to create new drainage channels.

At present, glaucoma is not curable. Treatment often can relieve the elevated intraocular pressure and prevent or slow the progression of optic nerve damage, but existing damage cannot be reversed nor vision restored. Nor is there an accurate way of determining which individuals, with either normal or elevated intraocular pressure, are at risk for developing open-angle glaucoma with visual loss. It is therefore very important to discover ways to detect glaucoma at its very earliest stages, so that treatment may be instituted promptly and damage to the optic nerve may be minimized.

## PROGRAM STRUCTURE

Research in the National Eye Institute's Glaucoma Program is classified under seven subprograms which provide the basis for the organization of this report. Four subprograms are listed under the general heading "Open-Angle Glaucoma," because

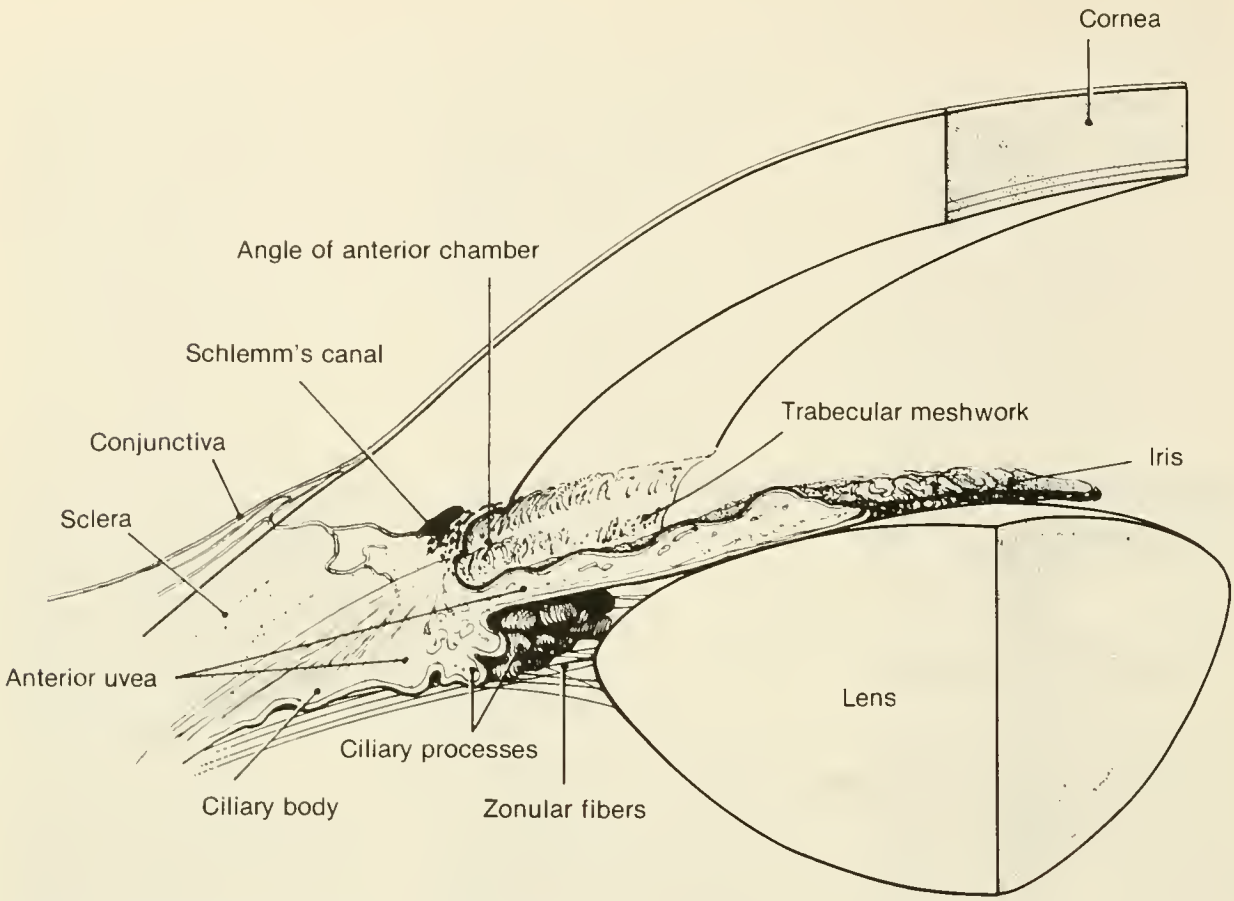


FIGURE. Schematic section of the human eye showing structures discussed in this chapter. The iris and ciliary body constitute the anterior portion of the uveal tract.

it is the most common type of the disease; however, much of the information derived in the first four subprograms applies not only to open-angle glaucoma, but to all types of glaucoma.

**Primary Open-Angle Glaucoma**

1. Etiology, Epidemiology, Management, and Therapy
2. Aqueous Humor Dynamics: Inflow
3. Aqueous Humor Dynamics: Outflow
4. The Optic Nerve

**Other Glaucomas**

5. Angle-Closure Glaucoma
6. Developmental, Congenital, and Infantile Glaucomas
7. Secondary Glaucomas

## *Primary Open-Angle Glaucoma*

It is estimated variously that 50–80 percent of all glaucoma in the United States is of the open-angle type. Primary open-angle glaucoma is characterized by elevated intraocular pressure, an anatomically open angle, and typical patterns of change in the visual field and in the appearance and topology of the optic disc. It is generally considered to be caused by a defect in the aqueous humor outflow system, either physical collapse of the filtration channels or by materials clogging the trabecular meshwork to increase resistance to outflow. Damage to a given optic nerve results from exposure to a level of intraocular pressure which that particular nerve cannot tolerate. The treatment of open-angle glaucoma is to lower intraocular pressure, and generally begins with drugs; if medical therapy fails, laser treatment or surgery is used. In a majority of patients, glaucoma can be controlled by such treatment.

**Epidemiology, Etiology, Management, and Therapy**. This subprogram is concerned with epidemiologic investigations including those to elucidate risk factors, both for the disease and for losing

vision once it is diagnosed; clinical studies of glaucoma; and clinical trials of promising new therapies. The prevalence of open-angle glaucoma increases sharply with age, and for reasons still unexplained, both the incidence and the severity of the disease appear to be greater in blacks than in whites. The genetic or environmental factors that may predispose individuals to glaucoma remain to be elucidated, as do the factors such as the time of diagnosis, type of treatment, and patient compliance with prescribed therapy that may affect the course and severity of the disease. As new types of therapy emerge, it is important that they be investigated through carefully designed clinical research and then evaluated in controlled clinical trials.

**Aqueous Humor: Inflow.** It is important to understand how aqueous humor is produced by the ciliary epithelium, because most drugs and some surgical techniques used to control intraocular pressure act to diminish aqueous humor formation. Research in this subprogram may include basic cellular and physiologic studies to determine the mechanisms of drug action, studies with primates, and clinical observations to determine the effectiveness of treatments in controlling glaucoma. The long-term physiologic effects of severely diminished aqueous humor outflow on the tissues nourished by it—especially the lens and corneal epithelium—also need to be defined.

**Aqueous Humor: Outflow.** In open-angle glaucoma aqueous humor outflow is hindered, although no obstruction of the trabecular meshwork is apparent upon direct or microscopic observation. Research is under way to determine what processes maintain the normal physical and structural integrity of the meshwork, and how they are changed in open-angle glaucoma. Studies of outflow of aqueous humor may be focused on cellular mechanisms of drug action, ultrastructure of the drainage tissues, the effects of drugs on the physiology of human eyes, and improving surgical or laser procedures to facilitate outflow.

**The Optic Nerve.** Experimental studies of the optic nerve are aimed at determining the events that initiate the pathologic changes typical of glaucoma and defining the course of the damage. Damage to the optic nerve occurs when intraocular pressure reaches a level that cannot be tolerated by a particular nerve.

It is extremely important to learn how to detect the earliest signs of optic nerve damage in glaucoma and to predict which ocular hypertensives are likely to develop glaucoma, so that they may be treated prophylactically. Research is also needed to explain the variability in response of an individual optic nerve to a given level of pressure.

## *Other Glaucomas*

**Angle-Closure Glaucoma.** In the United States, angle-closure accounts for an estimated 10–20 percent of glaucoma cases. The immediate cause of angle-closure glaucoma (sometimes called narrow-angle glaucoma) is known: contact of the iris with the trabecular meshwork blocks filtration of the aqueous humor and precipitates a rise in intraocular pressure. This occurs in eyes with certain predisposing anatomic characteristics; however, not all susceptible eyes suffer angle-closure attacks. Although this condition can be alleviated effectively by either conventional surgery (iridectomy), or laser treatment (iridotomy), investigators need to learn how to determine which eyes are in danger of closure and should be treated prophylactically with drugs, surgery, or laser, and the indications for each type of treatment.

**Congenital, Developmental, and Infantile Glaucomas.** Most cases of congenital and infantile glaucoma are developmental, due to anatomic anomalies. Others occur secondary to other ocular conditions. Thus, glaucoma in infants and children is due to impaired outflow of aqueous humor which may be caused by anatomic maldevelopment or be a consequence of other eye diseases. Some of these types of glaucoma are quite difficult to treat and, if treatment is unsuccessful, can lead to lifelong visual impairment or blindness. This group of diseases is responsible for about 5 percent of all blindness in children in this country.

**Secondary Glaucomas.** Secondary glaucomas occur as a result of other ocular diseases that damage the aqueous humor outflow system, trauma, and certain vascular or inflammatory diseases. Although some of these diseases are quite rarely seen, they are important and often difficult to treat types of glaucoma that lead to blindness more often than does open-angle glaucoma. Secondary glaucomas account for an estimated 10 percent of all glaucoma, but because of their severity they account for a significant portion of all surgery for glaucoma.

A common form of secondary glaucoma, neovascular glaucoma, occurs in some people with retinal vascular diseases, particularly diabetic retinopathy. In this condition, new fibrovascular tissue grows on the iris and ciliary body, then spreads over the filtering area of the chamber angle. Ultimately, synechiae (adhesions) fix the iris against the trabecular meshwork and close off the angle. As more diabetics live longer—thanks to improved medical care and understanding of the disease—the incidence of neovascular glaucoma may increase. Conventional medical and surgical therapy often cannot control neovascular glaucoma but may be useful in controlling pain. Much remains to be learned about the factors that affect the fibrovascular proliferation

and how it may be controlled. Panretinal laser photocoagulation of the new vessels in the retina seems to limit their proliferation into the iris. A number of laboratories are attempting to characterize factors that may cause or play a role in neovascularization, particularly inhibitors of the process.

Another common type of glaucoma may follow longstanding uveitis or other inflammatory conditions of the anterior segment of the eye. Glaucoma secondary to inflammation may be caused by angle-closure due to posterior or anterior synechiae, glaucomatocyclitic crisis, or chronic iridocyclitis. The roles of prostaglandins and other mediators of inflammatory processes or associated cellular products in regulating intraocular pressure remain to be elucidated.

The etiology and therapy of each secondary type of glaucoma need special attention. Some are amenable to study in animal models, and all require careful clinical study. Because many of the individual secondary glaucomas are rare, carefully coordinated collaborative research studies will be needed to gain useful natural history and treatment data.

# ORGANIZATION OF THE PLAN

Each chapter in this report begins with an introduction that highlights the importance of the research field or disorder it addresses. This is followed by a list of subprogram objectives, an overview of current research support, a review of recent research accomplishments, and a discussion of current research needs and opportunities. This analysis culminates in a list of the Panel's recommendations for the Program Base and for Program Development Priorities within the subprogram.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Each chapter concludes with a table that shows the number and dollar amount of research grants supported in each of these areas in FY 1981 and the number and estimated costs of projects the Panel recommends for funding by FY 1983. For a detailed discussion of the planning process used to develop these recommendations see *Volume One, The 1983 Report of the National Advisory Eye Council.*

# PROGRAM GOALS

- To prevent loss of vision in all types of glaucoma by improved means of detection, diagnosis, and therapy.
- To understand the basis of optic nerve damage in glaucoma and the reasons why the susceptibility to a given level of intraocular pressure varies in individual optic nerves.
- To describe the basic pathophysiology of the different types of glaucoma at the levels of cell, tissue, and organ, and how they may be altered therapeutically.
- To define the basic processes in the normal eye which regulate aqueous humor dynamics, and determine how drugs used or proposed for use in therapy interact with them.
- To develop predictive measures for the onset and development of glaucoma, and particularly the detection of very early optic nerve damage, with special emphasis on noninvasive techniques.
- To conduct epidemiologic studies of the different types of glacuoma, including both natural histories and responses to treatment.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In 1981, the National Eye Institute supported 87 grants for research on glaucoma at a total cost of $8,961,000. Eighty-seven percent of these funds supported studies either focused directly on problems specific to primary open-angle glaucoma or aimed at problems common to all types of glaucoma. Projects devoted specifically to angle-closure received 3 percent of National Eye Institute funds allocated for glaucoma research, childhood glauco-

mas received 1 percent, and secondary glaucomas received 9 percent.

Although considerable progress has been made in initiating research discussed in the Glaucoma section of the 1978–1982 National Vision Research Plan, other recommendations from that Plan have not been fulfilled. This is because either opportunities for research in these areas were not as great as envisioned, qualified investigators were not available, or areas of research then considered promising turned out not to be fruitful. For example, data suggesting the presence of genetic markers for open-angle glaucoma in peripheral cells could not be substantiated and thus no new projects in this area were initiated, no studies of the epidemiology of glaucoma were initiated, no studies of low tension or malignant glaucoma were proposed, and no research was proposed with the specific goal of developing means to protect the optic nerve.

On the other hand, when a new opportunity arose, investigators were ready to exploit it. For example, following the demonstration of the feasibility of growing trabecular meshwork cells in culture, a number of applications were submitted and several grants were awarded for the study of their properties. After it became apparent that laser trabeculoplasty was a promising means of treating open-angle glaucoma, the NEI received a proposal for a collaborative controlled clinical trial of this procedure. The application was approved and funded, and the trial will begin in 1983.

The present report was developed following an analysis of the glaucoma research currently supported by the NEI and other organizations, assessment of unfulfilled research areas described in the prior Plan, and consideration of new research needs and opportunities perceived by the Panel.

# RECENT ACCOMPLISHMENTS

## *Aqueous Humor Hydrodynamics: Inflow and Outflow*

A fundamental question about open-angle glaucoma concerns the basis of obstruction to aqueous humor outflow, and recent studies have focused upon the filtering area of the trabecular meshwork as the most likely site. Electron microscopic studies of trabecular meshwork specimens obtained during surgery for primary open-angle glaucoma have demonstrated accumulations of extracellular materials, glycosaminoglycans, which may play a role in the pathogenesis of outflow obstruction. A study of trabecular endothelial cell density in normal eyes showed a decrease in the number of cells per meshwork as a function of age, and in eyes with primary open-angle glaucoma the number of cells per meshwork seemed to be reduced below levels normal for their ages. The latter finding may be significant in defining the etiology or natural history of glaucoma.

Trabecular endothelial cells, which now can be grown in tissue culture and appear to maintain their normal functions, are a significant new tool for exploring normal cellular functions and pharmacologic reactions and how they may be altered in glaucoma.

Aqueous humor fluorophotometry, a technique for noninvasive study of aqueous humor dynamics is now coming into clinical use. It will aid researchers in clinical studies, and contribute to basic understanding of aqueous humor dynamics and drug effects on the processes involved.

## *Open-Angle Glaucoma*

Two new drugs have been introduced recently into glaucoma therapy. The beta-adrenergic blocking agent, timolol, is relatively free of ocular side effects and is effective in treating primary open-angle glaucoma alone or when supplemented with other classes of anti-glaucoma drugs. An NEI-sponsored five-year clinical trial is currently observing patients treated with timolol alone, or with timolol plus other antiglaucoma drugs to assess timolol's long-term benefits and ocular and systemic side effects. Dipivalyl epinephrine, a prodrug, is clinically effective and penetrates the eye more efficiently and produces fewer local and systemic side effects than its hydrolysis product, the active agent epinephrine.

Argon laser treatment of the trabecular meshwork (trabeculoplasty) is rapidly coming into use as a substitute for surgery in the treatment of primary open-angle glaucoma; the scarring caused by applying many small laser burns to the trabecular meshwork is thought to increase tension on the filtering area and thereby stretch it into a configuration favorable for improved aqueous humor filtration. An NEI-sponsored clinical trial will soon evaluate laser trabeculoplasty in comparison with conventional therapy in the treatment of open-angle glaucoma.

## *Optic Nerve Studies*

Studies of the mechanisms by which elevated intraocular pressure can damage the monkey optic nerve show that at increased pressure levels axonal transport in the nerve is diminished. Fluorescein angiographic studies have shown areas of reduced vascularity in damaged optic nerves, indicating that either an underlying ischemic mechanism or a

secondary vascular loss accompanies the loss of nerve fibers.

Methods devised for quantifying the optic disc configuration by stereophotogrammetry and its vascularity by densitometry and fluorescein angiography soon may be available for general clinical use. Several new types of automatic and semiautomatic perimeters are now available; some simply detect defects, others record quantitative data that can be used to detect any worsening of the status of individual patients.

Recent reports have suggested that glaucoma affects aspects of visual function other than the visual threshold measured by standard perimetry. For example, contrast sensitivity and color vision appear to be abnormal very early in the course of optic nerve damage in glaucoma; these or other psychophysical tests may also aid in the early detection of glaucoma.

### *Other Glaucomas*

The use of laser energy to relieve angle-closure by iridotomy (burning a hole in the iris) instead of the conventional surgical iridectomy is a significant clinical advance; laser iridotomy is a simple outpatient procedure that results in few complications.

Although much remains to be learned about developmental and congenital glaucomas, animal studies have provided useful information. Studies in birds may provide new insights into the pathogenesis of some developmental glaucomas. Anterior segment neovascularization and neovascular glaucoma may develop much less frequently in eyes treated with panretinal photocoagulation at appropriate stages of diabetic retinopathy than in untreated control eyes. Panretinal photocoagulation also may be beneficial after neovascular glaucoma develops, but before the angle is completely sealed, by causing regression of established anterior and posterior segment neovascularization.

A new microelectronic device, which fits into a bottle of eyedrops and records the hour of each use of the medication over a month's time, will be of great assistance in studies of patient compliance with therapeutic regimens.

A group of three diseases, essential iris atrophy, Chandler's syndrome, and the Cogan-Reese iris nevus syndrome are characterized by corneal endothelial dystrophy, progressive peripheral anterior synechiae, obstruction of aqueous humor outflow, and varying degrees of iris degeneration. These disorders appear to be variants of an "irido-corneal endothelial syndrome" and have been found to share a common histopathologic abnormality: overgrowth of the trabecular meshwork and iris by endothelial cells and Descemet's membrane.

Finally, a mechanism has been proposed to explain why the pigment is lost from the back of the iris in pigmentary glaucoma. There is strong evidence that in certain eyes contact between the zonular fibers and the iris causes pigment to be rubbed off as the pupil contracts and expands.

## RESEARCH NEEDS AND OPPORTUNITIES

### *Open-Angle Glaucoma*

Current medical therapy usually is effective in reducing intraocular pressure in open-angle glaucoma and may be useful in certain types of secondary glaucoma, but it does not reverse the underlying obstruction to aqueous humor outflow. If the fundamental details of outflow obstruction were understood, improved specific therapies could be devised to prevent the progress of the disease or cure it. Tissues from glaucoma patients at various stages of the disease are difficult to obtain, particularly in a form suitable for study. A tissue registry associated with eye banks could be used to arrange for suitable donor eyes to be collected under specified research protocols for preservation and distribution to glaucoma research centers.

Solid information is lacking on the epidemiology of glaucoma and possible risk factors associated with it. Many questions remain concerning the numbers of people having the various types of the disease, genetic and environmental predisposing factors, why some cases of ocular hypertension progress to optic nerve damage but not others, and why individual optic nerves are either susceptible or resistant to damage at varying intraocular pressures. Another especially important question is why glaucoma occurs more frequently, and is a much more severe disease, in blacks than in whites.

Low tension glaucoma is poorly understood; both basic studies to define the condition further and clinical studies to evaluate its treatment are needed. A controlled clinical trial to study the value of lowering intraocular pressure below "normal" levels in low tension glaucoma patients would provide valuable information about this condition.

New noninvasive devices for monitoring aspects of aqueous humor dynamics would enhance both the clinical management of glaucoma and studies of its basic pharmaco-physiologic mechanisms. Methods for continuous monitoring of intraocular pressure, and for controlled drug release would enable research clinicians to monitor closely their patients' conditions and responses to drugs and to develop improved treatments.

New quantitative fluorophotometric techniques for measuring aqueous humor formation are coming into clinical use, but they need to be refined for

more generalized application. Continuous short-term monitoring of aqueous humor flow in humans should provide valuable information about the physiology, pathophysiology, and pharmacology of aqueous humor formation. Also, analyses of all the forces involved in fluid flow into the eye across the various membranes of the blood-aqueous barrier are important for understanding the etiology and treatment of glaucoma. For example, questions that need to be answered are: What are the drug effects on pseudofacility (pressure-dependent aqueous humor formation)? Also, does the aqueous humor inflow rate vary with the circadian rhythm of intraocular pressure?

While investigators are learning more about the physiological, biochemical, pharmacological, and anatomical correlates of aqueous humor inflow, more information is required to provide a basis for improved means of controlling glaucoma. New types of drugs to enhance the outflow of aqueous humor should be developed. Improved modes of delivering drugs to specific targets in the eye should be developed. Drugs for topical application should penetrate the cornea readily and provide long-term efficacy in the treatment of glaucoma while having minimal and acceptable systemic or ocular side effects. Primates in particular should be studied, because their ocular anatomy and physiology resemble human eyes more closely than those of other animals.

Failure of glaucoma surgery, due to healing over of filtering blebs that allow drainage of aqueous humor, is poorly understood. The possibility that factors unique to the aqueous humor of some glaucoma patients stimulate cell growth should be explored. The increasing enthusiasm of physicians for laser treatment of the trabecular meshwork to improve aqueous humor outflow necessitates clinical studies of the safety and long-term efficacy of the various aspects of this procedure, including definitive studies for selecting eligible patients and developing optimal technical methods for laser therapy.

Further characterization of the biology of the trabecular meshwork should be undertaken on several different levels. The pharmacologic and physiologic effects of various categories of drugs on outflow resistance should be defined, and ultrastructural correlates of tissue responses should be identified using modern electron microscopic and histochemical techniques. Further development and application of tissue culture technology should permit more specifically targeted studies of trabecular endothelial cells and lead to a rationale for specific drug development.

The origin and roles of trabecular extracellular macromolecules, and how these materials affect outflow resistance in normal eyes and in glaucoma need to be defined. Although the trabecular meshwork is perfused with aqueous humor, investigators do not know if or how aqueous humor constituents affect its biological responses. The physiology and pharmacology of the posterior outflow (uveoscleral) routes are not well defined. Studies of fluid exchange processes in this region should suggest new therapeutic methods for enhancing aqueous humor outflow.

## *Optic Nerve*

Increased effort should be devoted to understanding how damage to the optic nerve is correlated with the level of intraocular pressure and to improving means for assessing the clinical status of the optic nerve head, the lamina cribrosa (the area of the sclera through which the optic nerve fibers leave the eye), local blood flow, and other physiologic indicators of the optic nerve's condition. To apply appropriate therapy, clinicians must be able to judge which eyes with high intraocular pressure will suffer damage. Such knowledge might lead to the development of methods other than pressure reduction to protect the optic nerve and reduce or reverse nerve damage.

New types of noninvasive measures of optic nerve status that would make possible the very early reliable diagnosis of glaucoma should be sought. Refinements of existing tests would also be of value; automated perimeters should be evaluated critically in the clinic. A variety of psychophysical tests for various aspects of visual function, which could be more readily quantified than standard visual field testing, should be explored as possible means for early detection of glaucoma.

Studies, especially those involving primates, should continue to focus on mechanisms of nerve damage. It is extremely important to develop a reliable experimental model of chronic human glaucoma in which the overall abnormal physiologic effects could be studied. Only when the mechanisms of damage are defined, can research on pharmacologic means to alter the pathophysiologic process be undertaken profitably.

Epidemiologic studies are particularly important for defining factors important to the genesis and progression of nerve damage in low tension glaucoma, open-angle glaucoma, and ocular hypertension.

## *Other Glaucomas*

The underlying anatomic abnormalities and mechanisms of angle-closure must be defined and subclasses of the disease identified if optimal therapeutic procedures are to be selected. Criteria should be developed for reliable determination of sub-classes of angle-closure. Risk factors for the predisposition of some narrow-angled eyes to angle-closure remain

to be elucidated, and improved provocative tests to predict closure are needed.

New types of lasers, such as the Q-switched YAG, which disintegrates rather than burns tissue, are coming into use for creating iridotomies; these should be evaluated in comparison with the argon laser. The value of chronic miotic treatment in preventing angle-closure should be evaluated. Better criteria are needed for deciding when filtration surgery rather than iridectomy is required, as when a diagnostic choice must be made between open-angle glaucoma with a narrow angle and angle-closure glaucoma. Other clinical studies are needed to ascertain the possible benefits of breaking synechiae, and to determine if the initial therapy for angle-closure should be a miotic drug, laser treatment, or surgery.

Knowledge of the development of the primate anterior chamber angle is based mainly upon scattered light microscopic examinations of limited numbers of specimens. Modern techniques should be used to re-examine the embryonic development of the normal chamber angle. Chamber angle development in animal fetuses should be experimentally altered and the histologic appearance of the induced abnormalities correlated with those found in human developmental glaucoma.

Means must be devised to enable more accurate measurements of intraocular pressure in children without use of anesthesia, and new measurement techniques suitable for use in awake children must be developed, including noncontact tonometry, standardized methods for evaluating the anterior chamber angle, and improved objective methods for evaluating visual function. New drugs and special drug delivery systems for treating children should be developed and tested in carefully controlled clinical studies. A prospective randomized study should be conducted to compare the efficacy and safety of goniotomy and trabeculotomy, and the indications for each in treating infantile and childhood glaucomas.

Because the pathophysiology of ocular neovascularization is poorly understood, investigators need to define carefully the epidemiology and natural history of anterior segment neovascularization and neovascular glaucoma. A reliable animal model for neovascular glaucoma is needed, although existing models of the underlying vascular diseases might be exploited in relevant studies. Studies of possible neovascularization factors and the mechanisms by which cells in non-ocular tissues may produce angiogenic or anti-angiogenic factors may be relevant to the problems of neovascular glaucoma. Promising new pharmacologic agents should be evaluated and the efficacy of panretinal photocoagulation and goniophotocoagulation in preventing and treating growth of new vessels on the iris and preventing or limiting glaucoma should be studied systematically. Careful clinical studies of the modified trabeculectomy and valve insertion procedures also are needed.

Studies relating to the etiologic and pathogenetic mechanisms of ocular inflammation will be relevant to understanding and treating of glaucoma secondary to uveitis. The roles of inflammatory cells and their products in the pathogenesis of inflammatory glaucoma need clarification, and the effectiveness of new specific anti-inflammatory drugs should be determined.

Because a number of secondary glaucomas share as a common histopathologic feature abnormal growth of the corneal endothelium and Descemet's membrane over the trabecular meshwork, investigators need to know what control mechanisms normally stimulate and inhibit this endothelial growth and why it is stimulated in such diverse pathologic conditions as essential iris atrophy, Chandler's syndrome, iris nevus syndrome, posterior polymorphous corneal dystrophy, and angle recession.

# RESEARCH TRAINING NEEDS

A major problem in glaucoma research is that presently only a few highly qualified people are being attracted into the field. A disappointingly small number of individual fellowships (National Research Service Awards) have been dedicated to glaucoma research, a total of six in 1979–1981. Only three trainees in glaucoma research have been supported on institutional training grants during that period. More well-trained clinicians must be attracted into glaucoma research and encouraged to undertake advanced training in research design and clinical trial methodology. Also, means must be developed of bringing cell biologists, physiologists, and scientists in other disciplines into collaboration with ophthalmologists, so that their combined knowledge may be applied to solving the important problems in glaucoma. A large number of academic positions for clinical glaucoma research specialists remain vacant. Thus, there is an overall need for an increase in recruitment, manpower development, and training in research techniques to increase the number of qualified glaucoma research personnel.

# SUMMARY OF 1983–1987 RECOMMENDED PROGRAM DEVELOPMENT PRIORITIES

- Develop improved therapies for all types of glaucoma.
- Conduct controlled clinical trials to evaluate new medical treatments for controlling intraocular pressure in all types of glaucoma.
- Conduct controlled clinical trials to evaluate new surgical methods for treating glaucoma, such as laser trabeculoplasty in open-angle glaucoma and filtering valve implantation in neovascular glaucoma. Determine reasons for failure of filtering surgery.
- Conduct epidemiologic studies of all types of glaucoma; identify genetic and environmental risk factors and determine factors leading to loss of vision due to glaucoma. Evaluate the role of genetic and racial factors in determining the incidence and severity of open-angle glaucoma.
- Develop new noninvasive means for measuring aqueous humor hydrodynamics for use in experimental and clinical studies of normal and glaucomatous eyes of man and nonhuman primates; devise new noninvasive tests to assess the status of the optic nerve and to detect the earliest signs of glaucoma.
- Investigate basic biochemical, physiologic, and pharmacologic processes controlling aqueous humor production and outflow in isolated cells and tissues, using emerging techniques of cell biology. Determine the etiology of optic nerve damage and investigate means of protecting the optic nerve in glaucoma.
- Develop cooperative programs to study and treat the glaucomas of children.
- Study the secondary glaucomas to define for each the etiology and natural history and test specific methods of treatment. Of special importance is increasing knowledge of neovascular glaucoma and glaucoma following ocular inflammatory conditions.

# IMPLEMENTATION OF THE PLAN

The individual, investigator-initiated, NIH research project grant continues to be the National Eye Institute's predominant and highest priority funding mechanism. Therefore, the successful implementation of the recommendations of the Glaucoma Panel, as well as those of the other Panels that have contributed to *Vision Research—A National Plan: 1983–1987*, will depend largely upon investigators submitting grant applications for research in the scientific areas the Panel has identified for emphasis. Because scientific merit, as evaluated by the traditional NIH peer review system, will continue to be the principal determinant of which approved grant proposals the NEI will fund, those approved applications having the best "priority" scores assigned by NIH initial review groups, will be funded. Applications with mid-range scores will be paid as funds are available; however, some may be specifically designated by the Council as having "High Program Relevance" (that is, fulfilling one of the Plan's recommendations, especially in an area of research considered to be underfunded), and are recommended for placement in a more favorable position for funding. Applications with poorer scores will not be funded—even if they propose research on a topic the Panel has judged to be in need of additional or new support (Chart).

By using such a system, NEI supports scientific excellence, innovation, and creativity while carrying out its mission of supporting research aimed at alleviating blindness and visual disability. The National Advisory Eye Council will monitor the responses of the research community to the recommendations in the Plan as well as new research advances and developing opportunities, and recommend to the NEI staff on a regular basis what further implementation measures or changes in program priorities may be required. For further discussion of the Plan's development and implementation, see *Volume One, The 1983 Report of the National Advisory Eye Council.*

# RESOURCE REQUIREMENTS

The following table presents a summary of the Panel's estimates of the number of grants necessary to carry out its recommendations for each of the Glaucoma subprograms in FY 1983. The actual number and cost of grants funded in each subprogram in FY 1981 (the base year of the Plan) are

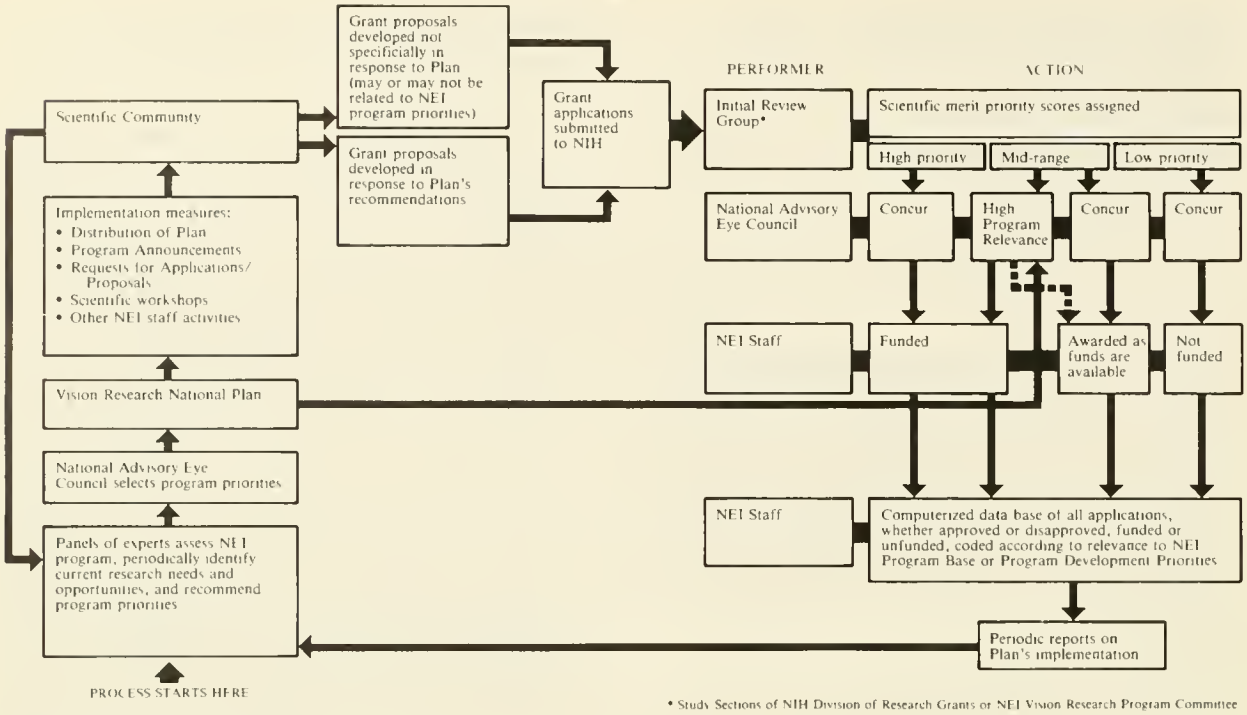


CHART. National Eye Institute Program Planning System. Both the NIH scientific merit priority scores and the program priorities established in the National Plan help determine which grant applications NEI will fund. All applications with high scientific merit priority scores are funded regardless of their relevance to program priorities. Some applications with mid-range scores and judged to be highly relevant to program priorities are singled out and placed in a better funding position than they would have been on the basis of the score alone.

shown in the first column. The second column indicates the number of additional (or fewer) grants the Panel believes should be funded in each subprogram through the end of FY 1983, based on an analysis of current research and of future needs and opportunities. The total number of grants for FY 1983 for each subprogram indicated in the third column is the estimated sum of new and continuing awards to be made in that year along with an estimate of their cost.

For example, the first line of the table shows that 7 grants were actually awarded in FY 1981 for studies relating to "Etiology, Epidemiology, Management, and Therapy." Because about one-third of all NEI grants terminate in any given year, in making its estimates for FY 1983 the Panel assumed that about 2 of the 7 projects funded in FY 1981 would terminate FY 1981, thereby making funds available for new or renewal grants in this subprogram in FY 1982 and that another 2 would terminate in FY 1982. The Panel then judged that an additional 6 grants would be required by FY 1983 to meet its recommendations in this subprogram. Therefore, of the total of 13 projected awards in this subprogram for FY 1983, approximately 3 would be ongoing and 10 would be new or renewal awards to be funded during FY 1982 and FY 1983.

The actual number of grants funded in this and the other subprograms may of course be either more or less than these projections indicate, depending on the quality, kind, number, and costs of the grant applications NEI receives and the availability of funds. Concerning funding, it must be emphasized that the six Panels' dollar estimates for FY 1983 do not necessarily indicate what the actual National Eye Institute extramural research budget will be for that year. However, because the Panels' estimates are based upon detailed documentation of projected research needs and costs, it is hoped that those in the Executive and Legislative branches of the Government who make the final decisions concerning the NEI budget will use them in making informed judgments about the resources required for the support of vision research. In making these estimates the Panels took into account the following factors for each category of research considered:

- Degree of relevance to the program's goals and objectives
- Current level of support by NEI and other organizations

- Recent research accomplishments
- Potential for future development
- Availability of trained manpower
- Likelihood of significant progress over the next three to five years.

The Panel recognizes that in addition to scientific judgments, social, economic, and political considerations will shape the final NEI budget for each year. Therefore, no attempt has been made in this report to make detailed resource estimates beyond FY 1983, although the Council has projected an overall budget for the NEI through 1985 (*Volume One*). The Panel understands that in the future, the Council, with the assistance of scientists knowledgeable in areas of research supported by the NEI, will provide more detailed estimates for the remaining years of the Plan based on actual budgetary experience and ongoing analyses of research progress. In this way the Plan will be modified as necessary on a year-to-year basis.

At the end of each chapter in this report, subprogram resource tables show how the estimates shown in the following summary table have been derived from estimates for each research category included in each subprogram's Program Base and the Program Development Priorities.

# SUMMARY RESOURCE TABLE

(Dollars in Thousands)

| Subprograms/Areas | FY 1981 Grants* Cost | | Panel Recommendation FY 1983 Add. Grants Cost | | Panel Recommendation FY 1983 Total Grants Cost** | |
|---|---|---|---|---|---|---|
| 1. PRIMARY OPEN-ANGLE GLAUCOMA | | | | | | |
| a. Etiology, Epidemiology, Management, and Therapy | 7<br>$723 | (8%) | 6<br>$785 | (17%) | 13<br>$1,508 | (10%) |
| b. Aqueous Humor Dynamics: Inflow | 27<br>$2,885 | (30%) | 7<br>$1,059 | (20%) | 34<br>$3,944 | (27%) |
| c. Aqueous Humor Dynamics: Outflow | 24<br>$2,273 | (27%) | 7<br>$1,323 | (20%) | 31<br>$3,596 | (25%) |
| d. The Optic Nerve | 16<br>$1,771 | (18%) | 6<br>$781 | (17%) | 22<br>$2,552 | (18%) |
| 2. OTHER GLAUCOMAS | | | | | | |
| a. Angle-Closure Glaucoma | 3<br>$155 | (3%) | 3<br>$541 | (9%) | 6<br>$696 | (5%) |
| b. Developmental, Congenital, and Infantile Glaucomas | 2<br>$137 | (2%) | 3<br>$443 | (9%) | 5<br>$580 | (4%) |
| c. Secondary Glaucomas | 11<br>$836 | (12%) | 3<br>$788 | (9%) | 14<br>$1,624 | (11%) |
| **Total** | **90**<br>**$8,780†** | **(100%)** | **35**<br>**$5,720** | **(100%)** | **125**<br>**$14,500** | **(100%)** |

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Glaucoma program for FY 1983 is $116,000.

† Does not include one conference grant and one grant for scientific evaluation supported by Glaucoma program funds.

# PRIMARY OPEN-ANGLE GLAUCOMA

# 1

# ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY

## INTRODUCTION

*PRIMARY OPEN-ANGLE GLAUCOMA* is a chronic ocular disease characterized by (1) elevated intraocular pressure due to impaired outflow of aqueous humor, (2) anatomically open anterior chamber angles, (3) distinctive changes in the appearance of the optic disc (acquired excavation and pallor), (4) characteristic nerve fiber layer and visual field loss, and (5) bilateral involvement of the patient's eyes. There are two other conditions which have some of the same features of POAG: "low tension" glaucoma, in which field loss and disc changes are seen in the absence of elevated intraocular pressure at the time of diagnosis, and "ocular hypertension," in which pressure is elevated at the time of diagnosis, but no changes in disc or field are apparent.

In prevalence surveys, primary open-angle glaucoma accounts for 50 to 80 percent of all cases of glaucoma.[1,2] Over one-half the people with primary open-angle glaucoma found in these surveys were unaware of their condition.[1]

Primary open-angle glaucoma is a major health problem, and all types of glaucoma together constitute one of the major causes of blindness and visual impairment.[3] About 1.5 million people have glaucoma, and as many as 5 to 10 million may have ocular hypertension.[4] It is not known how many of the latter will develop open-angle glaucoma.

The prevalences of both elevated intraocular pressure and primary open-angle glaucoma rise dramatically with advancing age. The prevalence of ocular hypertension rises from approximately 2 percent at ages under 40 to 9 percent at ages over 70. The prevalence of primary open-angle glaucoma rises even more steeply with advancing age, from .02 percent for those 40–49, to 2 to 3 percent for those over the age of 70. Consequently, the proportion of those with elevated pressure who have optic disc and visual field damage also rises with age, from about 2 percent in the age group 40–49 to about 20–30 percent for those over the age of 70 (see Table).[1,2,5–8] It has been estimated that the incidence of glaucoma in blacks is considerably higher than in whites. Also, it is a common clinical impression that the course of the disease is more severe in blacks than in whites.

The fact that the proportion of those with elevated pressure who have disc and field damage increases with age seems to indicate a greater susceptibility of older people to optic nerve damage, rather than a cumulative effect of pressure over time. Among patients with similar degrees of ocular hypertension, the elderly have a greater risk of developing field defects in 5–12 years than young patients.[9] The reason that the optic nerve is more susceptible to damage in the elderly is not known. Apart from age there is significant individual variation in the susceptibility of optic nerves to glaucomatous damage. Thus, some people suffer optic nerve damage at relatively low pressures, while others withstand considerable pressure elevation for many years without damage. In population-based studies, only one-tenth or less of those with elevated intraocular pressure had suffered field loss,[2,6,7] and data from longitudinal studies suggest that only one-tenth of the remaining ocular hypertensives would develop field loss within 10 years.[10] Conversely, one-third to one-half of patients who did have glaucomatous disc and field changes at the time the study began had intraocular pressures of less than or equal to 20mm Hg and were initially classified as having low tension glaucoma.[1,2,6,7] In one study

**The Bedford Study***

| Age in Years | Percent Prevalence POAG | Percent Prevalence IOP>21 mm Hg | Ratio |
|---|---|---|---|
| < 40 | — | 2.0 | — |
| 40-49 | .02 | 2.0 | .01 |
| 50-59 | .31 | 3.5 | .09 |
| 60-69 | .90 | 4.5 | .20 |
| 70-79 | 2.82 | 5.5 | .51 |

*Glaucoma prevalence is based upon 45 eyes, 3 of which had IOP under 21 mm Hg. IOP over 21 mm Hg prevalences interpolated from Figure 3 of the Bedford Study.[1]

**The Framingham Eye Study***

| Age in Years | Prevalence POAG | Prevalence IOP>21 | Ratio |
|---|---|---|---|
| < 65 | .4 (.2) | 6.2 (6.2) | .06 (0.03) |
| 65-74 | .8 (.5) | 9.3 (9.3) | .09 (0.05) |
| > 75 | 1.8 (.8) | 8.7 (8.7) | .21 (0.09) |

*Glaucoma prevalence is based upon 40 eyes, 19 of which had IOP under 21 mm Hg. Data in parentheses recalculated to conform with data presented in the Des Moines table below.

**The Des Moines Study***

| Age in Years | Percent Prevalence POAG | Percent Prevalence IOP>21 mm Hg | Ratio |
|---|---|---|---|
| 40-49 | .3 | 10 | .03 |
| 50-59 | 1.50 | 15 | .1 |
| 60-69 | 2.70 | 20 | .14 |
| 70-79 | 6.3 | 20 | .32 |

*Glaucoma prevalence is based upon 60 eyes which had IOP over 20 mm Hg.

TABLE. The Proportion of People with Elevated Intraocular Pressure Who also Have Visual Field Loss Increases with Age: Results of Three Studies.

one-half of these later were found to have elevated intraocular pressure, defined as over 22mm Hg, the rest remained within the normal intraocular pressure range.[2]

Low tension glaucoma is thought to include several separate subtypes of glaucoma, some of which show progressive disc and field changes requiring treatment, and others which are nonprogressive even without treatment. Some nonprogressive cases can be attributed to documented previous anterior ischemic optic neuropathy,[11] hemodynamic crises,[12] or resolved steroid-induced elevation of intraocular pressure. Some of the progressive cases later are found to be associated with variable but generally elevated intraocular pressure, some are due to neurological disease mimicking glaucoma,[13] and others are associated with demonstrable vascular insufficiency (reduced central retinal artery pressure on ophthalmodynamometry), and some constitute a group that may be called true low tension glaucoma. The only available therapy for this condition is to lower the pressure to subnormal levels.[14] The mechanism of optic nerve damage in true low tension glaucoma is unknown, but a vascular etiology is suggested by its frequent association with disc hemorrhages.[15]

At present, the basic reasons for varying individual susceptibility to optic nerve damage in glaucoma are unknown. However, some empirical and clinically useful observations are: (1) past damage predicts future damage unless the intraocular pressure is lowered,[16] (2) damage to one eye significantly increases the likelihood that the other eye will be damaged unless therapy is begun (29 percent of untreated fellow eyes will develop field loss in an average of five years[17]), and (3) a family history of visual field loss from glaucoma puts a glaucoma patient at higher risk for nerve damage than those without such a history.[18] There is also some evidence suggesting that concurrent cardiovascular disease,[19] diabetes,[19] myopia,[20,21] or a rising intraocular pressure[22] are associated with greater risk of optic nerve damage. Blindness from glaucoma may be as much as eight times more common in blacks than in whites.[3]

Although the mere presence of elevated intraocular pressure correlates weakly with the presence of glaucomatous nerve damage, the prevalence of damage rises with the degree of pressure elevation. Thus, in two clinical studies about 6 percent of patients with moderately elevated pressure had damage, while 28–36 percent had damage at pressures greater than 30mm Hg, and 57 percent with pressures of 40mm Hg or more.[19,23]

The exact nature of the impairment of aqueous humor outflow in primary open-angle glaucoma is unknown. Study of the disease is limited by lack of an adequate animal model and by the fact that diseased human tissue rarely can be obtained from eyes in the early stages before secondary changes due to glaucoma or drugs may have occurred.

Electron microscopic comparisons of trabecular meshwork specimens removed during surgery for primary open-angle glaucoma with specimens from normal eyes (obtained postmortem or removed during life because of other ocular problems) have shown that in glaucoma there are accumulations of extracellular material in the trabecular meshwork and thickening and collapse of the supporting collagenous trabecular beams.[24,25] The extracellular materials appear to consist in part of proteoglycans and glycosaminoglycans, since they can be digested

by specific mucopolysaccharide-splitting enzymes.[25] It is not known whether these morphologic changes are a primary aspect of the disease process (for example, abnormal accumulation or diminished turnover of these materials), are secondary to therapy, or occur secondary to a more distal obstruction of aqueous humor outflow (for example, due to a dysfunction of the intracellular channels of the endothelial cells of the inner wall of Schlemm's canal[26] or to a collapse of Schlemm's canal[27]).

A possible clue to the etiology of the obstruction of aqueous humor outflow in open-angle glaucoma is the observation that administration of glucocorticoids induces a reversible elevation of intraocular pressure in some people, especially those with primary open-angle glaucoma.[28,29] Trabecular specimens from patients who developed irreversible steroid glaucoma while on long-term steroid therapy have extracellular materials in the trabecular meshwork similar to those seen in eyes with primary open-angle glaucoma.[30] Consequently, there is considerable interest in studying the mechanism by which steroids affect the outflow pathways. An understanding of the biochemical or cellular basis of the pressure elevation in steroid glaucoma may yield insights into the pathogenesis of primary open-angle glaucoma.

The pathophysiology of optic nerve damage and visual field loss in glaucoma is not completely understood (see Chapter 4, "The Optic Nerve"). Circumstantial evidence suggests that ischemic damage to the optic nerve head is the essential factor,[31] but alternatively the damage might be due to mechanical compression of optic nerve axons at the lamina cribrosa.[31] An understanding of the mechanisms of optic nerve damage in glaucoma and ability to monitor its progress obviously would be beneficial in making therapeutic decisions. At present, clinicians cannot predict which ocular hypertensives are at particular risk of nerve damage and need to be committed to a lifetime of antiglaucoma therapy.

# SUBPROGRAM OBJECTIVES

- To identify the site(s) of obstruction of aqueous humor outflow in eyes with primary open-angle glaucoma and its cellular and biochemical basis.
- To determine the epidemiology and natural history of ocular hypertension and primary open-angle glaucoma.
- To improve means of monitoring intraocular pressure, optic disc, and visual field and of identifying clinical features that are associated with or predictive of optic nerve damage.
- To determine the effectiveness and side effects of current medical and surgical treatments for primary open-angle and low tension glaucoma, and to develop treatments that are safer, more effective, and longer lasting, or that permanently arrest glaucoma.
- To determine why persons visually impaired from glaucoma lost vision.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981 the National Eye Institute supported seven grants, at a total cost of $723,000, that dealt specifically with primary open-angle glaucoma, and additionally many grants supported in the subprograms discussed in Chapters 2, 3, and 4 that are related directly to research on this disease. Two grants were devoted to improving methods for clinical monitoring of aqueous humor dynamics. One investigator worked with an animal model. Three studies were concerned with clinical investigations of potential anti-glaucoma drugs. There was one study of patient compliance with treatment regimens.

# RECENT ACCOMPLISHMENTS

In the Framingham Eye Study, a middle-aged to elderly cohort was examined for the prevalence of glaucoma and other eye diseases. The Study also investigated whether any of the variables previously measured during the Framingham Heart Study were associated with these eye diseases. As in earlier investigations, a strong relationship was found between age and the prevalence of ocular hypertension and glaucoma.[6] In the Framingham,[6] Dalby,[7] and Ferndale[2] studies, one-third to one-half of people with glaucomatous field defects had initial intraocular pressures in the normal range, though one of these followup studies found that half of the low tension glaucoma patients subsequently had elevated intraocular pressures.[2]

Electron microscopic studies of trabecular meshwork specimens obtained during surgery for primary open-angle glaucoma and steroid-induced glaucoma have shown excessive accumulations of

extracellular materials,[24,25,30,32] which might play a role in the pathogenesis of outflow obstruction.

Considerable attention has been focused on the cells of the trabecular meshwork. Trabecular endothelial cell density in nonglaucomatous eyes was shown to decrease as a function of age.[33,34] The density of cells per meshwork from eyes with primary open-angle glaucoma also decreased with age, and at a higher rate than in normal eyes. One may speculate that primary open-angle glaucoma is an abiotrophy, similar to corneal endothelial dystrophy. Further study of trabecular tissues from patients with ocular hypertension and early primary open-angle glaucoma is essential for testing this hypothesis.

Human trabecular endothelial cells have been grown in culture in laboratories in the United States[35] and Germany.[36] Trabecular endothelial cells synthesize proteoglycans, glycosaminoglycans, fibronectin, collagen, and laminen in tissue culture,[37,38,39] in vivo,[40] and in whole trabecular meshwork in vitro.[41] Cultured trabecular endothelial cells and surgical specimens of trabecular meshwork contain endogenous hyaluronidase and specific beta-adrenergic and glucocorticoid receptors.[42–44] Glucocorticoids decrease the rate of hyaluronate degradation in cultured trabecular cells, leading to its excess accumulation.[45] Continuing studies with cultured pure cell lines may disclose which aspects of the biology of the meshwork are abnormal in patients with open-angle glaucoma.

Animal studies have shown that although aqueous humor outflow is not an energy dependent process,[46] it can be affected by inhibitors of glycolysis and by sulfhydryl agents.[47,48] These findings might have therapeutic importance.

The concept that collapse of Schlemm's canal[27] may play an important role in decreased outflow facility in glaucoma received support from studies showing that the resistance to circumferential flow in Schlemm's canal is markedly increased when the intraocular pressure rises to greater than 30mm Hg[49] and from measurements of canal width in perfused eyes.[50]

The National Advisory Eye Council's 1977 program planning report noted several putative genetic markers associated with, and possibly predictive of, susceptibility to primary open-angle glaucoma. However, further investigations of several of these leads have yielded negative results. Early reports of associations of specific HLA antigens with primary open-angle glaucoma[51,52] were not confirmed in other investigations.[53–55] Three groups of investigators reported an increased cellular sensitivity to glucocorticoids in lymphocytes from patients with primary open-angle glaucoma, as compared with normal individuals,[56–58] but these observations were not confirmed.[59–61] This phenomenon later was found to be a stress-related artifact, since increased sensitivity also was found in patients hospitalized for surgery for other ocular conditions.[62] Further, neither specific glucocorticoid receptor numbers nor affinities differed from normal in the lymphocytes of primary open-angle patients.[63] Analogous studies of skin fibroblasts from primary open-angle glaucoma patients and controls matched for age, race, and sex also showed no differences in glucocorticoid receptor numbers, affinities, or function.[64]

Nevertheless, since most primary open-angle glaucoma patients are sensitive to the intraocular pressure-raising effects of glucocorticoids, cellular hypersensitivity to glucocorticoids may exist in primary open-angle glaucoma, not as a generalized defect, but specifically in the ocular tissues involved in the regulation of intraocular pressure. Glucocorticoid receptors have been found in trabecular cells[42,43] and in the ciliary body and iris using both biochemical[65] and radioautographic[66] techniques. These receptors translocate from the cytoplasm to the nucleus in response to physiological doses of active glucocorticoids, as do receptors in known steroid-responsive tissues.[67] Radioautographic studies using trabeculectomy specimens from patients with open-angle glaucoma have demonstrated specific binding of glucocorticoids in trabecular meshwork cells and endothelial cells of Schlemm's canal.[44] Enzymes involved in steroid metabolism also have been found in ocular tissue. A glucocorticoid A-ring reductase (which irreversibly metabolizes glucocorticoids to biologically inactive products) has been reported in the rabbit iris.[68]

Major advances have been achieved in the therapy of glaucoma with new drugs, better uses of existing drugs, and the use of laser treatment. The beta-adrenergic blocking agent timolol is an effective therapeutic agent for primary open-angle glaucoma[69–74] and its effects are either partially[75–77] or completely additive to those of other classes of antiglaucoma drugs. Timolol acts predominantly by decreasing aqueous humor production.[78] Dipivalyl epinephrine, a clinically effective prodrug of epinephrine,[79,80] causes fewer local[81] and systemic side effects than its parent compound.[82]

Recent clinical investigations have demonstrated that lower than customary doses of carbonic anhydrase inhibitors often provide equivalent therapeutic benefit, and with considerable reduction in side effects.[83,84] Tests of serum carbon dioxide-combining power and urinary pH are a useful means of monitoring acute and chronic compliance in the use of carbonic anhydrase inhibitors.[85]

Vanadate, an intracellular blocker of sodium-potassium ATPase, decreases aqueous humor production in rabbits and monkeys.[86] The dose-response relationship, toxicity, and possible therapeutic use of vanadate in man remain to be established.

A major advance in the treatment of medically resistant cases of primary open-angle glaucoma

employs argon laser treatment of the trabecular meshwork (trabeculoplasty).[87] Many groups of investigators have reported excellent results using this technique as a substitute for surgery.[87–89] An NEI-sponsored collaborative clinical trial to establish the long-term efficacy and limitations of laser trabeculoplasty as a potential substitute for early medical therapy has been initiated.

A minute filtering valve has been developed for use in eyes with intractable glaucoma associated with either extensive conjunctival scarring or angle-closure due to neovascularization,[90] but further clinical testing of its effectiveness is required.[90]

Hourly measurement of intraocular pressure over a 24-hour period has confirmed that a circadian rhythm of intraocular pressure exists in normal persons and that its amplitude is more pronounced in glaucoma patients. Preliminary results suggest that the intraocular pressure is at its nadir during sleep,[91] implying that it may be unnecessary for some glaucoma patients to arise at night to take medication.

Research continues on the mechanisms that govern circadian intraocular pressure variation; neural[92] and humoral[93] mechanisms also remain under investigation.

Longer-term monitoring of intraocular pressure has been performed with a strain gauge imbedded in a soft contact lens.[94]

A newly developed microelectronic device, which fits inside an eyedrop bottle, records the hour each time a patient uses glaucoma medication over a period of a month. Retrieval of the device by the investigator makes it possible to prepare a computer printout of the stored information for studies of patient compliance with the treatment regimen.[95]

# RESEARCH NEEDS AND OPPORTUNITIES

Current medical therapy of primary open-angle glaucoma is usually effective in reducing intraocular pressure but does not reverse the underlying obstruction of aqueous outflow, which would be needed for a cure. It is attractive to think that if the fundamental details of the causes of outflow obstruction were understood, specific and effective therapies might be devised to cure or prevent the disease.

Basic research on primary open-angle glaucoma is often hampered by the difficulty of obtaining affected tissue for study. Because there is no valid animal model for open-angle glaucoma, human tissues must be studied. Unfortunately, little tissue can be obtained for study from glaucoma patients in the early stages of the disease before secondary changes occur; for the most part only end-stage tissues have been examined.

The shortage of suitable material for study might be overcome by establishing glaucoma patient registries at eye banks. Clinically well-characterized patients of all ages should be recruited who have various stages of classic primary open-angle glaucoma and who demonstrate the extremes of optic nerve sensitivity to the effects of intraocular pressure (that is, ocular hypertensives who have endured long-term elevation of intraocular pressure without damage and patients with low tension glaucoma whose visual field has continued to deteriorate at normal pressures).

The concept of glaucoma patient registries might be developed through a National Eye Institute-sponsored workshop. With NEI assistance, protocols could be developed for patient recruitment and classification, and kits designed for prompt fixation or transport of eyes. The potential donors should be given a well-designed identification bracelet that would identify the disease, drugs taken, ophthalmologist's telephone number (which might also benefit the patient in a medical emergency), and the eye bank's telephone number to call in the event of the patient's death. Efforts would then be made to inform ophthalmologists and eye banks of the program and encourage their participation in donating and delivering tissues to qualified research laboratories.

Trabecular meshwork, ciliary body, and optic nerve tissues should be made available for anatomic, histochemical and autoradiographic studies, biochemical analyses, and tissue culture work. Age-matched eye-bank eyes would serve as controls. Special attention should be given to determining the cellular or biochemical basis of outflow obstruction, secondary and drug effects on the angle tissues and ciliary body, and the mechanism or mechanisms (vascular and/or mechanical) of damage to the optic nerve.

Case-control and cohort studies are needed to seek factors that characterize people destined to remain ocular hypertensives and those destined to develop the disc and field changes of glaucoma, so that cost-effective mass screening and well-targeted prophylactic therapy might be initiated. It might be especially valuable to compare cases of progressive low tension glaucoma with ocular hypertension cases.

The epidemiology and subclassification of low tension glaucoma should be studied. In addition, the benefit of lowering the pressure to the subnormal range in progressive low tension glaucoma needs to be evaluated in a collaborative controlled clinical trial. Also, as discussed in Chapter 4, the factors that make the optic nerve susceptible to damage at low intraocular pressure need to be defined and therapies to protect the nerve sought.

The degree of effectiveness of medical, laser, and surgical therapies for primary open-angle glaucoma in preventing further visual loss should be tested in long-term prospective clinical trials or retrospective studies.[96]

The epidemiology of blindness and visual disability from glaucoma needs further study, especially to determine the basis for the apparent racial (genetic) differences between blacks and whites in the prevalence and severity of the disease. Population-based case-control studies of glaucoma patients should be conducted to determine why some lose vision while others do not. This study should be designed to discover the relative contributions to visual loss of patients of (1) failure to be aware of encroaching visual loss; (2) failure to seek medical attention promptly; (3) improper diagnosis, monitoring, or treatment of the disease; (4) failure of patient compliance with prescribed therapy; and (5) failure of therapy to halt the glaucoma.

The possible benefits to ophthalmologic research of the current revolution in microelectronics should be explored. The glaucoma compliance monitor described above could be used to test the effectiveness of compliance measures such as patient education and wrist alarm watches. Methods for continuous monitoring of intraocular pressure should be refined and used in conjunction with the compliance monitor to determine the actual effectiveness of prescribed treatment regimens and perhaps eventually be coupled with a drug delivery system.

Advances in knowledge of tissue growth factors should be applied to discovering why filtering operations for open-angle glaucoma fail. For example, samples of primary and secondary aqueous humor taken at the time of filtering surgery, or cataract surgery in patients with functioning filtering blebs, or at surgical revision of acutely failed filtering blebs could be studied for the presence and level of growth factors which stimulate Tenon's and scleral fibroblasts.

The optimal uses of laser trabeculoplasty should be further investigated in prospective controlled collaborative clinical trials.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Etiology, Epidemiology, Management, and Therapy," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

## *Program Base*

- Develop and exploit naturally occurring models of impaired aqueous humor outflow.
- Improve methods for monitoring aqueous humor outflow, especially noninvasive techniques.
- Conduct clinical studies on the effects and mechanisms of drug actions and on the effects of drug dosages, dosing schedules, and drug combinations; conduct clinical trials of promising new drug treatments for primary open-angle glaucoma.

## *Program Development Priorities*

- Establish eye donor programs so that appropriately obtained and preserved human tissues from well-characterized glaucoma patients will become available for clinicopathologic correlations and cell biology studies.
- Study the epidemiology and natural history of low tension glaucoma.
- Evaluate the treatment of low tension glaucoma, identify and characterize its subclasses, and evaluate the need for and effectiveness of treatment in each.
- Conduct case-control and cohort studies of blindness and visual impairment from open-angle and other types of glaucoma to find why vision was lost (for example, early lack of symptoms, failure to seek medical attention, improper diagnosis and treatment, noncompliance, failure of therapy).

- Study reasons for patient compliance and noncompliance with drug regimens prescribed for treatment of primary open-angle glaucoma.
- Pursue research leads toward development of a lasting therapy for primary open-angle glaucoma.

# RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## PRIMARY OPEN-ANGLE GLAUCOMA

ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Develop and exploit naturally occurring models of impaired aqueous humor outflow. | 1 | 0 | 1 |
| B. Improve methods for monitoring aqueous humor outflow. | 1 | 0 | 1 |
| C. Conduct clinical studies on drug actions and clinical trials of new drug treatments for primary open-angle glaucoma. | 4* | 0 | 4 |
| **Program Development Priorities** | | | |
| A. Establish eye donor programs to obtain tissue from glaucoma patients. | 0 | 1 | 1 |
| B. Study the epidemiology and natural history of low tension glaucoma. | 0 | 1 | 1 |
| C. Evaluate the treatment of low tension glaucoma. | 0 | 1 | 1 |
| D. Conduct case-control studies of blindness and visual impairment from open-angle and other types of glaucoma. | 0 | 1 | 1 |
| E. Study patient compliance with drug regimens prescribed for treatment of primary open-angle glaucoma. | 1 | 1 | 2 |
| F. Pursue research leads toward development of lasting therapy for primary open-angle glaucoma. | 0 | 1 | 1 |
| **Subtotal Grants** | **7** | **6** | **13** |
| **(% of Program)** | **(8)** | **(17)** | **(10)** |
| **Total Estimated Cost** | **$723,000** | **$785,000** | **$1,508,000** |

*Includes two single-center clinical trials: Timolol: A New Drug for the Treatment of Glaucoma and Carbonic Anhydrase Inhibitors in Treating Glaucoma.

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# 2

# AQUEOUS HUMOR DYNAMICS: INFLOW

## INTRODUCTION

*MAINTENANCE OF A NORMAL* intraocular pressure depends upon the balance of all fluid exchanges at different locations in the eye. Either an increase in the rate of aqueous humor production or a decrease in the rate at which aqueous humor leaves the eye will cause an increase in intraocular pressure. Of major importance is the fluid exchange across the large surface area of the ciliary body epithelium, which is the site of aqueous humor formation.[1] Ultimately, the aqueous humor exits from the eye through both the trabecular meshwork and the posterior (uveal or unconventional) outflow pathways (see Chapter 3, "Aqueous Humor Dynamics: Outflow").

The ciliary body consists of two cellular epithelial layers: a layer facing the posterior chamber containing nonpigmented cells, and a layer underlying it containing pigmented cells. Embryologically, the two layers are derived from an infolding of the optic cup. This results in the basal membrane of the nonpigmented cells facing the posterior chamber. This basal membrane is covered by an internal limiting membrane which is continuous with that of the retina and iris. Tight junctions connect the lateral surfaces of the nonpigmented cells near their apices, constituting the "blood-aqueous" barrier. The nonpigmented cells, which are considered to be the primary source of aqueous humor, contain many energy-producing mitochondria and have numerous basal surface invaginations, which increase their surface area. Anatomical studies of the entire ciliary epithelium indicate the presence of a complex integration of cells; knowledge of how drugs affect the individual cell layers will be useful in developing better medications for treating glaucoma.

The blood supply to the ciliary body arises from both the major circle of the iris and the anterior ciliary arteries. Its venous drainage is mainly by way of the vortex veins, although some blood exits through the intrascleral veins into the episcleral veins. Numerous vessels pass along the crest of each ciliary process, and capillaries extend along the leaflets of each process. The fluid that ultimately becomes aqueous humor is derived from these blood vessels. The sympathetic nerve supply of the uveal blood vessels, which may influence the formation of aqueous humor, is carried by the short ciliary nerves. The parasympathetic innervation of the iris and ciliary body arises from the ciliary ganglion.

The physiologic mechanisms for aqueous humor formation include both ultrafiltration and secretion. Ultrafiltration is the result of fluid pressure gradients within the various ocular compartments, but the individual contributions to these pressure gradients have not yet been measured. Ultrafiltration depends upon both systemic blood pressure and intraocular pressure because increased intraocular pressure reduces aqueous inflow. The cellular secretion component is better understood than the ultrafiltration component. For example, the concentrations of sodium, potassium, chloride, and bicarbonate ions, some amino acids, glucose, and other organic compounds in aqueous humor are maintained by specific transport systems in the ciliary epithelium.[1–5]

Aqueous humor has a lower protein concentration than serum because the blood-aqueous barrier excludes large molecules. The existence of a barrier implies that certain substances do not move passively or bidirectionally through cell membranes and that specific active transport systems are required for moving some ions and molecules from the bloodstream into the ocular tissues, or for moving

substances from the aqueous humor into tissues and blood vessels. The barrier also keeps materials transported across ciliary epithelial cells from leaking back into the ciliary body.

Various inhibitors of enzymic processes decrease aqueous humor inflow by different amounts,[6-8] providing additional evidence for active secretory processes. Carbonic anhydrase inhibitors are administered systemically to treat glaucoma and may reduce the rate of aqueous humor formation by as much as 50 percent.[8] Other substances that may be of clinical value are $Na^+$ $K^+$ ATPase inhibitors, especially ouabain[9] and vanadate,[7] which have reduced intraocular pressure in experimental animals after intravitreal and topical administration, respectively. Several nonspecific metabolic inhibitors such as dinitrophenol and cyanide also decrease intraocular pressure.[6]

The anion transport systems of the anterior uvea bear a strong relationship to those of the kidney and liver, and their properties may be studied in parallel with the kidney systems. The larger quantities of kidney tissue available for research may be used for pilot studies applicable to research on uveal pharmacologic processes.[4,5,10] Also, the process of aqueous humor formation closely resembles the formation of cerebrospinal fluid. Better understanding of aqueous humor formation by ciliary tissues can be gained by applying knowledge obtained from study of the physiology of similar membrane systems and by adapting new technical procedures to studies in the eye.

Looking toward improved therapeutic applications, progress has been made in identifying specific adrenergic and cholinergic receptors in the entire ciliary body and defining receptor linkages to the cellular metabolism of cyclic nucleotides and receptor responses to drugs.[11,12] Recent studies[13-15] have indicated that drug effects on fluid flow into and out of the eye are more complex than originally conceived; the mechanisms of drug actions are still understood only superficially.

Prostaglandins and related naturally occurring autacoids released following ocular injury, inflammation, and allergic reactions have been of interest because they cause increased aqueous humor inflow.[16] These effects are more prominent in rabbits[17,18] than in primates and humans.[19]

In animals, aqueous humor formation has been studied primarily by invasive techniques that monitor the dilution of a radioactive substance or dye to measure the rate of fluid inflow. Indirect methods have also been used, such as changing the intraocular pressure by applying a suction cup to the eye or by calculations from tonographic data.[1] For studies in man, noninvasive methods must be used, such as measuring fluorescein turnover in the aqueous humor.[13-15,20] These recently described techniques appear to be sound, although results differ from those obtained from tonographic data. The two techniques must be reconciled. It should now be possible to study the hydrodynamics of normal and abnormal aqueous humor flow in man directly and measure accurately the effects of various therapeutic measures. For example, intraocular pressure normally varies in a circadian rhythm; in eyes with glaucoma the amplitude of the variations is much greater than in normal eyes,[21] but the governing mechanisms are not understood. Although glaucoma is considered to be a disease or malfunction of the aqueous outflow system, it has been suspected but not proved that some of the variation in intraocular pressure may be due to changes in aqueous inflow. Also, the rate of aqueous humor formation diminishes with age, but to what extent is not known. This effect should now be measured accurately.

Aqueous humor formation can be reduced therapeutically by drugs and surgery. Timolol[22] is a new beta-adrenergic blocking agent that has become widely used in the treatment of glaucoma. It does not affect pupil size or accommodation, and most patients tolerate it well. Prodrugs, which require conversion in the body to active compounds to produce pharmacological activity, are showing promise as improved drugs. For example, dipivalyl epinephrine, which is converted to epinephrine in the anterior chamber,[23,24] is now being used in place of epinephrine in the treatment of glaucoma. Dipivalyl epinephrine has certain therapeutic advantages over epinephrine because it penetrates the cornea more readily and is effective in lower doses, thereby reducing the systemic side effects that accompany the direct use of epinephrine. When a carbonic anhydrase inhibitor is required, methazolamide is now often used in place of acetazolamide because it may be used at lower doses and produces fewer side-effects. This has alleviated considerably the problem of patient compliance. Osmotic agents, administered intravenously or orally, are sometimes used to treat angle-closure glaucoma; fluid is removed from the anterior chamber and deposited in the intraocular blood vessels.

An unnaturally low intraocular pressure, hypotony, is in effect the opposite of glaucoma. Because the aqueous humor provides nutrients to ocular tissues, and a normal intraocular pressure provides mechanical support for the retina and choroid, hypotony can produce disastrous effects on the uvea, retina, cornea, and lens. Any study of aqueous humor dynamics, and its abnormalities, should include studies of the mechanism(s) and effects of hypotony and means of restoring a normal rate of aqueous humor formation.

# SUBPROGRAM OBJECTIVES

- To understand the roles played by fluid exchange, flow, and transport mechanisms in regulating inflow of aqueous humor and determining intraocular pressure.
- To determine how the processes responsible for the entrance of fluid into the eye may differ from normal in glaucoma, ocular hypertension, hypotension, and hypotony.
- To develop improved treatments to alter the rate of inflow of fluid into the eye.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981, the National Eye Institute supported 51 grants specifically for studies of the hydrodynamics of the eye, 27 of which emphasized inflow studies at a total cost of $2,885,000. Some laboratories are investigating anatomical aspects of the blood-aqueous barrier including the ciliary epithelium and iris, and the embryological development of the barrier. Animal models of glaucoma in the rabbit and dog are being examined by physiological, biochemical, and pharmacological studies. In several laboratories, the cholinergic pharmacology and the adrenergic and cyclic nucleotide pharmacology of the iris-ciliary body are being studied in various animal species. Fluid and anion transport systems of the ciliary epithelium are being examined with reference to aqueous inflow and removal of anions from the eye. Prostaglandin metabolism in the iris and ciliary body is under study, and one laboratory is studying the phospholipid metabolism of the iris and ciliary body. Other specific aspects of aqueous humor inflow, such as in hypotony or after intraventricular injection of pharmacologic substances, are under study.

The clinical effects of newly developed adrenergic drugs and frequently used aqueous humor inflow inhibitors are being examined in detail. Other drugs that affect intraocular pressure are under study in both animals and man, including corticosteroids, prostaglandins, and marihuana components (both cannabinoids and water-extracted material). Drug delivery using liposomes is under investigation in an experimental system. Thus, a wide range of investigations on aqueous humor inflow is supported.

# RECENT ACCOMPLISHMENTS

Advances have been made in defining anatomical and physiological factors in the regulation of intraocular pressure, and major new drugs to reduce aqueous humor inflow have been introduced. New noninvasive methods to measure aqueous humor dynamics may make it possible to correlate data from humans with those from animals and to observe the immediate physiologic effects of drugs in humans.

## *Anatomic Studies*

The blood-aqueous barrier and cellular permeability are both of paramount importance in determining aqueous humor inflow and how drugs affect it. Many types of intercellular junctions, including gap junctions, have been identified between the nonpigmented epithelial cells of monkey ciliary epithelium, indicating that the cells are joined in a metabolic syncytium.[25,26] An initial attempt has been made to correlate the ultrastructure and permeability of iris vessels with beta-adrenergic drug functions in the rat eye by observing how drugs affected tracer distribution between blood and tissues.[27,28] Cyclocryotherapy, which destroys the ciliary epithelium by freezing a portion of its circumference, has been used to reduce intraocular pressure.[29] However, the benefit and duration of effect of this procedure are often uncertain. Cryogenic injury to monkey ciliary epithelium diminished aqueous humor formation, and histologic examination revealed pigmented cells were more severely damaged than nonpigmented cells.[30] However, intraocular pressure returned to normal following the regeneration of nonpigmented ciliary epithelial cells,[30] which may explain why cryotherapy sometimes alleviates glaucoma only temporarily. The ciliary epithelial nonpigmented cell layer also regenerates after disruption by hypertonic osmotic solutions.[31,32]

## *Physiologic Studies*

Hypotony has long been thought to be due to decreased aqueous formation in experimental ciliochoroidal detachment, retinal detachment, or cyclodialysis. Recent studies in monkeys with experimental ciliochoroidal detachment have shown that despite an intraocular pressure reduction of about 6 mm Hg, the rate of aqueous humor formation is normal.[33] Instead, the reduced intraocular pressure is induced by an increased uveo-vortex aqueous humor outflow by way of the suprachoroidal space, which allows a bulk flow of fluid posteriorly and reabsorption by way of the choroidal vasculature.

Regional blood flow, which may affect aqueous humor formation, has been measured in the rabbit eye at intervals after topical application of drugs, and time-dependent changes have been observed. One hour after administration to both normal and sympathectomized eyes, at a time when the intraocular pressure was unchanged, several adrenergic agonists decreased blood flow in the iris and ciliary processes.[34] However, at three hours after epinephrine administration, when intraocular pressure was reduced, ciliary process blood flow was normal, and iridial blood flow had increased, possibly due to the increased prevailing perfusion pressure. A reduction in blood flow through the iris and ciliary processes of the monkey eye, lasting six hours, has been reported following the topical application of l-epinephrine.[35] Topically applied pilocarpine increased blood flow through the iris, ciliary processes, and ciliary muscles of monkey eyes by about 150 percent, suggesting that blood flow is mediated by vascular muscarinic cholinergic receptors.[36] Retinal blood flow decreased after topical epinephrine administration in aphakic rabbit eyes.[37]

Intracranial stimulation of the rabbit oculomotor nerve caused a reduction in iris and ciliary process blood flow (implying a vasoconstrictive effect), which was potentiated by indomethacin, a prostaglandin inhibitor.[38] In sympathectomized rabbits, oculomotor nerve stimulation caused a longlasting vasodilation.[39] Stimulation of the rabbit fifth cranial nerve caused an increased blood flow to the iris and ciliary processes, breakdown of the blood-aqueous barrier, and elevated intraocular pressure attributed to released Substance P.[40] These studies provide scattered clues that blood flow rates in iris-ciliary tissues affected by neurotransmitters, neuroactive peptides, and modulators are important in mediating fluid exchanges (and hence aqueous humor formation). However, much additional research is needed to clarify the details of the normal reactions of these substances in controlling blood flow in the ciliary body and how drugs may affect such reactions.

Orally administered carbonic anhydrase inhibitors, used in the treatment of glaucoma to decrease aqueous humor formation, often produce several adverse systemic side effects. Attempts to understand the mechanisms of these side effects and find means of managing them have included dose reduction, substitution among drugs in this class, and administration of sodium bicarbonate to reduce systemic acidosis. Although bicarbonate may relieve side affects and thereby improve compliance with carbonic anhydrase inhibitor therapy, it does not affect the control of intraocular pressure.[41] Systemic alkalosis increases, and acidosis decreases, the rate of aqueous formation in rabbits.[42]

Fluorophotometry, a noninvasive technique used to measure aqueous humor flow rate, has reached a stage in which clinical studies in unanesthetized subjects can be effectively undertaken, although presently at only a few specialized clinical research centers. The apparent validity of this technique in measuring aqueous humor turnover has enabled investigators to study drug effects on human subjects. For example, when combined with data from other procedures such as tonography, detailed analyses can be made of the complex effects of drugs on the systems controlling ocular hydrodynamics in humans.[13-15,20]

## *Pharmacologic Studies*

Drugs that have primarily alpha-adrenergic effects cause an initial rise in intraocular pressure in rabbits, followed by an ocular hypotensive response. Drugs with beta-adrenergic activity have only an immediate ocular hypotensive effect, and $beta_2$-agonists are particularly potent.[43] The d-isomers of various adrenergic agonists, generally thought to be physiologically inactive, cause a fall in rabbit intraocular pressure accompanied by limited vascular or cardioactive effects, suggesting that they may have a useful role in ocular therapy.[44] Chronic administration of a beta-adrenergic drug to rabbit eyes produced successively smaller effects on IOP over time,[45] an adaptation phenomenon similar to the tolerance that develops in humans treated with beta-adrenergic drugs. This response to daily topical epinephrine administration in rabbits is suppressed with flurbiprofen, a prostaglandin synthetase inhibitor,[46] indicating a possible prostaglandin mediation of adaptation to adrenergics.

Several clinical studies of the concurrent administration of epinephrine and timolol have indicated that despite their opposing pharmacologic mechanisms of action, when given together the drugs decrease intraocular pressure more than either alone—at least in the short term.[14,15,47] The additional decrease in intraocular pressure is greater when timolol is administered to eyes that have already received epinephrine than vice versa. The results of these short-term experiments are puzzling in terms of current knowledge of basic adrenergic pharmacology. The additive effects appear to diminish over time, and the benefits of long-term mixed therapy in man remain to be determined.

Vanadate ion, an intracellular regulator of ATPase activity, reduces rabbit intraocular pressure by decreasing aqueous humor formation and may provide a means of reducing intraocular pressure in glaucoma.[7,48] A number of studies are beginning to define anti-glaucoma drug actions at the cellular level. The density of both alpha- and beta-adrenergic receptors has been measured in the iris-ciliary body of the rabbit after various medical or surgical procedures.[49,50] The density of beta-adrenergic receptors appears to be inversely related to the level

of adrenergic stimulation. However, the rate of synthesis of cyclic adenylic acid (cAMP, the intracellular mediator of beta-adrenergic receptor activation) does not necessarily parallel the changes in receptor density or intraocular pressure. A single administration of timolol inhibited the beta-adrenergic stimulation of cAMP synthesis by the rabbit iris-ciliary body, but within three hours the tissue regained its ability to produce cAMP when challenged in vitro with isoproterenol.[51,52] This short-lived effect in rabbits is in contrast to the prolonged pressure-lowering effect of timolol in humans. Future studies with primate eyes or cultured human cells may shed light on the reasons for this difference.

Also puzzling are the observations that cAMP levels in rabbit aqueous humor increase within one hour after topical epinephrine treatment (a response normally associated with beta-stimulatory drugs), which coincides with the early increase in intraocular pressure rather than the pressure-lowering effect that occurs later,[11,53,54] and that administration of cAMP alone decreases intraocular pressure. Timolol blocks the immediate cAMP increase caused by epinephrine, but not the later epinephrine-induced fall in intraocular pressure, thereby dissociating the changes in cAMP level from the hypotensive effects of epinephrine. Clearly, much more remains to be learned about the cellular and chemical bases of the ocular adrenergic responses, especially to these drugs which are commonly used in the treatment of glaucoma.

The supersensitivity or subsensitivity of tissues to commonly used anti-glaucoma drugs is of great clinical interest. Epinephrine appears to restrict either the number or availability of adrenergic receptors, probably by uncoupling or desensitizing the activation of adenyl cylase by guanyl regulatory protein and decreasing the activity of the beta-receptors which modulate their interactions, and consequently decreasing the beta-physiologic response.[52,53] The site of adrenergic supersensitivity does not appear to reside in the ciliary epithelium. This conclusion is based on the observation that adrenergic agonists increase the permeability of the ciliary epithelium in normal, but not in sympathectomized eyes, even though the whole eye is supersensitive to low doses of agonist.[55]

A marked decrease in the cat's ocular response to cholinergic agonists occurs following development of adrenergic supersensitivity.[56] The loss of inhibitory sympathetic input to the iris sphincter caused by adrenergic sympathectomy is thought to leave the cholinergic input unopposed due to removal of the normal antagonism, thereby leading to cholinergic subsensitivity. Continuous treatment of monkey eyes with echothiophate, a cholinesterase inhibitor, produced a subsensitivity to the miotic effect but not to the hypotensive effect of pilocarpine.[57] This suggests that two populations of acetylcholine receptors may exist, one in the iris sphincter and a second in the ciliary muscle, with pilocarpine acting as a muscarinic agonist on the iris and an antagonist on the ciliary muscle. Also, evidence for two classes of acetylcholine-binding sites in iris-ciliary tissues has been obtained using receptor-ligand assays.[58] Whether cells in normal eyes and in those with glaucoma respond differently to transmitters remains to be seen.

Both norepinephrine and acetylcholine significantly increase the breakdown of triphosphoinositide (TPI) in the iris,[59,60] and this effect can be blocked by atropine (a cholinergic blocking agent) and phentolamine (an alpha-adrenergic receptor blocker) respectively.[59,60] Surgical ganglionectomy also appreciably increases the TPI breakdown,[60] as do low concentrations of calcium ion ($Ca^{++}$).[61] The $Ca^{++}$ effect appears to be due to an increased $Ca^{++}$ flux across the muscle membrane mediated by agonist-receptor activation. The TPI breakdown could result in changes in membrane structure, which could increase the permeability to sodium and potassium ions, leading to membrane depolarization.[62] The TPI effect is sensitive to sodium ion.[63]

Iris muscle also incorporates arachidonic acid into its glycerolipids which are the source of prostaglandins and other physiologically active derivatives.[64] This conversion is stimulated by norepinephrine in a dose-dependent manner, which indicates a possible link among glycerolipids, prostaglandins, and adrenergic receptors.[65] In the iris and other ocular tissues, the prostaglandins, thromboxanes, and prostacyclins have been identified as metabolites of arachidonic acid; as yet there is no information about leucotrienes.[66–68] The biologically potent thromboxanes and prostaglandins have contrasting effects on blood vessels and platelets and possibly other tissues. The interaction between these metabolites in normal and pathological ocular conditions is under investigation. These substances and their metabolites may play a regulatory role in ocular tissues, especially during inflammatory reactions; the effects of inhibitors of the various steps in their biosynthesis are also under study in the eye.

Substance P may be the mediator of immediate ocular responses to trauma or irritants.[69] It is an endogenous peptide transmitter or mediator, which is released into the eye after stimulation of ocular sensory nerves, accompanied by miosis and inflammation.[70] Inflammation induces changes in ciliary body permeability. Other vasoactive[71] and adrenergic drugs,[72] including both $beta_1$- and $beta_2$-adrenergic agents,[73] directly effect the permeability of isolated rabbit ciliary epithelium. Acetylcholine increases both fluid secretion and passive permeability of the membranes, as does the peptide brady-

kinin, which may play a role in ocular inflammation.[71]

Since publication of a report that smoking marihuana caused a fall in intraocular pressure in some normal volunteers and glaucoma patients,[74] considerable research has been done with lipid-soluble cannabinoids. Delta-9-tetrahydrocannabinol (THC), identified with the major physiological and behavioral effects of marihuana, is the primary cannabinoid in marihuana, although there are about 40 other cannabinoids that may evoke other patterns of effects. Studies in rabbits have shown that these cannabinoids show a spectrum of activity in lowering intraocular pressure.[40]

Some cannabinoids have been given intravenously[75] and topically to man.[76-78] Topically administered THC has caused slight falls in intraocular pressure in treated and contralateral eyes,[78] and in some instances superficial corneal punctate keratitis.[76,78] It appears that the small drop in intraocular pressure in both eyes is caused by THC entering the systemic circulation by way of nasal-lacrimal drainage from the eye. However, two studies showed no fall in intraocular pressure following topical application of drops of 1 percent delta-9-tetrahydrocannabinol.[77,79]

Intravenous administration to rabbits of water-extracted material from marihuana leaf causes a marked fall in intraocular pressure at concentrations as low as 1 $\mu$g per animal.[80] A marked reduction in aqueous inflow is correlated with the fall in intraocular pressure.[81,82] These water-soluble non-cannabinoid extracts may be valuable tools in discerning the mechanisms of aqueous inflow and underlying pharmacology of aqueous formation, and may provide a basis for development of new drugs to reduce intraocular pressure.[83]

Intravitreal or close-arterial administration of cholera toxin leads to a pronounced and prolonged fall of intraocular pressure in rabbits.[84] Correlated with this fall is a sustained stimulation of cAMP synthesis in the ciliary processes.[85] Because this substance may prove to be another useful tool in identifying the processes underlying aqueous humor formation, the temporal effects of cholera toxin on changes in cAMP and cellular metabolic systems and intraocular pressure must be further investigated.

# RESEARCH NEEDS AND OPPORTUNITIES

It is evident that the physiological, biochemical, pharmacological, and anatomical correlates of aqueous humor inflow are becoming better understood but still require considerable additional study. Through the acquisition of such knowledge, new and improved methods for regulating the rate of aqueous inflow can be used in controlling glaucoma. Studies in human eyes are essential to adapt to human physiology the information from studies with animals (which often have different physiological and pharmacological properties), to further our understanding of the abnormalities in glaucoma and hypotony, and to evaluate potentially valuable drugs. New, noninvasive methods to study specific aspects of aqueous humor hydrodynamics and drug effects directly and safely in man are needed. However, certain experiments are either impossible or unethical to conduct in man, and for the answers to several important questions, research must continue in appropriate animal models. Studies in primates are particularly essential, because of important differences between the ciliary body physiology of man and that of rabbits and other common laboratory animals.

## *Anatomic Studies*

Further studies of the ultrastructure and cell biology of the ciliary epithelium are necessary to determine if differences exist between the cells of the pigmented or nonpigmented epithelium of the pars plicata and the pars plana. Also correlations should be sought between structures and physiological and biochemical functions to localize specific processes. Such knowledge could provide a morphological basis for the varied and multiple transport roles of the ciliary epithelia.

## *Physiologic Studies*

Knowledge of the forces underlying fluid movement from the blood vessels of the ciliary body into the posterior chamber is essential to a full understanding of aqueous humor inflow and its potential modification. The balance of the Starling forces in the ciliary body should be examined in detail, as has been done in the kidney,[86] to determine the role of ultrafiltration across the ciliary epithelium and the role of the ciliary body's vascular supply in controlling aqueous humor inflow. The large surface area of the ciliary vascular system affects regulation of the permeability of the local blood-aqueous barrier system, and this component's properties can be modified by drugs. Understanding the nature and type of cellular junctions in the ciliary vasculature and how they are affected by environmental or pharmacological factors is necessary to elucidate the factors regulating vascular permeability. Initial steps have been taken to determine the permeability of these vessels using graded sizes of tracers. Changes have been observed in the dimensions[87] and permeability[27,28] of iris vessels after drug

treatment. Studies using visible tracers in the living eye should be undertaken to determine the contribution of such vascular changes to aqueous humor inflow.

It is important to know how hydrostatic pressure is regulated in the various compartments of the eye and how inflammation may affect these processes. The roles of the chemical components of the extravascular tissue fluid in regulating the poorly understood ultrafiltration component of aqueous humor formation should be defined. Similarly, it is important to study the rate of blood flow in the anterior uveal tract. Because the principal method currently available for studying blood flow (the microsphere method) is cumbersome and invasive, noninvasive means are needed to study the effects of various drugs, hormones, and mediators on blood vessels and aqueous humor formation.

Another approach to understanding how aqueous humor is formed is to measure the fluid's bulk properties and its constituents. Studies have been performed in some species, but there are large gaps in knowledge about differences between concentrations of substances in the posterior and anterior chambers in many species, especially in man. The nature and composition of newly formed aqueous humor in the immediate environment of the ciliary processes is unknown, although there is some information for sodium and bicarbonate concentrations.[88] New methods for determining the local composition of freshly formed aqueous in an uncompromised eye are needed. It would be useful to study the ionic concentrations in cells and intercellular spaces, using the newest techniques of electron probe analysis to determine local concentration gradients in the microenvironment of the ciliary epithelium, and particularly the differences between the cells of the apex and those of the clefts of the ciliary processes.

The active transport mechanisms involved in ciliary cell metabolism and aqueous humor formation and secretion also need to be elucidated, and the effects of drugs (such as vanadate, ouabain, carbonic anhydrase inhibitors, and adrenergic agents) upon them need to be described. It is not known if any of the several known transport systems are linked to the co-transport of other chemical species. Interactions and competition among organic anions for transport processes are known to occur in the ciliary epithelium.[4,5,10] The relationship of ascorbate to fluid movement (due to local osmotic influence at the basal border of the nonpigmented epithelium), either as a possible coupling agent to other ion and fluid transport or as a metabolic stimulus, requires study. Transport by the ciliary epithelium of organic compounds from the anterior chamber is also important in excluding certain substances from the aqueous humor, including the products of inflammatory reactions, and in regulating aqueous humor inflow.

Little is known about the electrophysiology of the ciliary epithelium. A small electrical potential difference across the ciliary epithelium has been shown, but little is known about the possible differences between the cellular and the paracellular resistance of either pigmented or nonpigmented layers. Measurements under a variety of experimental conditions, such as using variable oxygen tension or various metabolic substrates, could delineate membrane characteristics and provide information about the pathways for ion and fluid movement across the ciliary epithelium and their contribution to aqueous humor formation. Likewise, very few experiments have attempted to determine the short-circuit current and ion transport systems across the ciliary epithelium.

Advanced technology should be used for determining the ionic dependence of the transport systems and their metabolic effects in human and primate tissues. The transport systems can be studied physically in several ways[89] and biochemically in the presence of various specific substrates and metabolic inhibitors. Such studies would provide information about how the systems are regulated and the effects of drugs on the individual transport processes involved in regulating aqueous humor formation.

Ion transport and the electrophysiology of the ciliary epithelium are coupled to fluid flow across the membrane. The dependence of the fluid flow on various metabolic processes and the nature of fluid flow in response to osmotic and hydrostatic gradients require further examination. Studies with isolated membranes would allow differentiation of membrane responses from blood flow contributions to transport. Still to be fully explained are the effects of endogenous substances that regulate normal ciliary physiology, or which are released in response to stimuli such as inflammation, on fluid flow across either the ciliary epithelium or its individual layers.

Increasing intraocular pressure suppresses the rate of aqueous humor formation, a phenomenon known as pseudofacility. However, it is not known if high intraocular pressure affects blood flow rate or blood pressure in the ciliary body vasculature, or if the suppression is purely a membrane effect caused by changing the hydrostatic gradients across the ciliary epithelium (the ultrafiltration component of aqueous humor formation). In a primate eye a sustained increase in intraocular pressure initially decreased inflow, but later the rate of aqueous humor inflow approached its normal value,[90] indicating some type of physiological adaptation. The nature of this adaptation has not been investigated. It is not known, for example, whether there is a compensatory increase in aqueous humor formation or wheth-

er the primary effect of high intraocular pressure is on the vasculature which, under neural control, slowly normalizes blood flow through an autoregulatory mechanism. These questions need to be answered, because continued elevation of intraocular pressure in glaucoma may lead to compensatory physiological changes, which in turn may alter the ocular response to various drugs.

Careful clinical studies also should be undertaken to evaluate the surgical procedures used to reduce aqueous humor formation, such as cryotherapy and laser burns to destroy the ciliary epithelium. These procedures may cause pain and discomfort, variable and unpredictable pressure-lowering effects, and effects on vision. Well-designed clinical studies of the surgical methods may lead to more definitive indications for their uses, definition of criteria for successful treatment, and improvements in their outcomes.

A study of the mechanisms underlying hypotony should be rewarding. Explaining the details of aqueous humor inflow and the outflow pathways in hypotony would provide better scientific understanding of the various types of hypotony and the overall phenomenon of fluid exchange within the eye, and lead to more effective ways to treat patients who suffer from this condition. Also, such information may lead to improved methods to control aqueous humor hydrodynamics in glaucoma. Many such studies could be conducted to good advantage in primates, but certain noninvasive methods (such as fluorophotometry) can be used now in humans with hypotony.

## *Pharmacologic Studies*

Effects of various adrenergic and cholinergic drugs on the iris-ciliary body have been measured, and tissue receptors for these drugs have been identified. However, these studies have used the whole tissue, including considerable amounts of smooth muscle, and do not provide information about drug effects on the ciliary epithelium alone. Interactions with the cAMP system of subclasses of adrenergic receptor systems of the ciliary epithelium require further investigation, especially with respect to cellular responses and the temporal effects of drugs on intraocular pressure and aqueous humor inflow. More pharmacologic studies are needed to define the effects of neuromodulators (neuropeptides), autacoids, steroids, inflammatory cell products, cannabinoid-related compounds and arachidonic acid derivatives (including prostaglandins) on intraocular pressure and on the responsiveness of the receptor systems. Biochemical responses of cells to drug-receptor interactions should be studied to explain the various pharmacological events that occur in the eye after the administration of exogenous or endogenous adrenergic or cholinergic compounds. The receptor populations of the iris and ciliary muscles play mixed roles in regulating ocular physiology; for example, cholinergically-induced ciliary muscle contraction improves outflow of aqueous humor but also produces undesirable changes in pupil size and accommodation.

The effects of adrenergic and cholinergic drugs on the metabolic activity of the cells of the ciliary epithelium remain unknown. Biochemical or metabolic changes may alter the regulation of aqueous humor inflow, and long-term use of such drugs to control aqueous formation may have undesirable effects. Other neuromodulators or neuroactive peptides, such as Substance P, may also affect the metabolism of these cells.

Pure lines of cultured pigmented and nonpigmented cells of ciliary epithelium would help in delineating many facets of their physiology, biochemistry, and pharmacology. Culture systems would be free of many of the factors that complicate analysis of function and pharmacology in the living eye or in isolated membrane systems that contain contaminating tissue elements. Viable isolated cells, which retain their original characteristics, should yield information about the respective roles of the pigmented and nonpigmented epithelial cell layers in the formation of aqueous humor, permitting studies to be conducted on ion substitution, fluid permeability, receptor density and modulation, cellular biochemistry, and responses to drugs of individual cell types.

Identification of the exact forces involved in fluid flow into the eye across the various membranes of the blood-aqueous barrier is particularly important for understanding the etiology and treatment of glaucoma. Important questions about the longstanding effects of elevated intraocular pressure on the rate of aqueous humor inflow and pseudofacility (suppressed rate of aqueous humor formation) remain unanswered. Another subject deserving additional research is the circadian rhythm of intraocular pressure, particularly to answer such questions as: Are there periods of increased or decreased aqueous humor inflow during the circadian variation of intraocular pressure? What are the biochemical and cellular origins of such fluctuations if they exist? Do drugs change the circadian rhythm?

At present, the best means of determining the rate of aqueous humor formation in the living animal eye are invasive methods based on dilution of radioactive compounds. But, these methods may exacerbate existing pathology, disturb the normal eye, or require infusion of fluids which cannot sustain the normal ocular physiology. Moreover, these methods can rarely be used in man.

Newer, quantitative photometric techniques of measurement are based upon the use of fluorescein.[13–15,20] These methods need to be refined to overcome some theoretical faults[91] and reconcile

discrepancies with data produced by the conventional approaches.[92–95] A good noninvasive method is needed for measurement of aqueous humor flow in humans continuously over short periods to provide information about the physiology, pathophysiology, and pharmacology of aqueous humor formation. Fluorescence photometry can also be used to study patients with hypotony.

It is also very important to understand the effects of the many endogenous compounds which act upon the processes contributing to aqueous humor inflow, and how drugs used in treating glaucoma interact with these processes. The pharmacological and biochemical bases for drug effects at cellular receptor sites in the ciliary epithelium need to be further defined. The interplay of drugs with the endogenous substances acting upon receptors of the ciliary epithelium and especially the changes in sensitivity of the adrenergic and cholinergic systems following the use of various drugs require careful study. For example, the chronic use of a particular drug (such as a beta-adrenergic antagonist) may alter the physiologic response of the tissue by inducing subsensitivity or supersensitivity to an adrenergic neurotransmitter. This possibility must be studied by careful systematic short- and long-term laboratory and clinical investigations.

The development of new drugs and modes of delivering them to specific targets in the eye is of great importance. A primary need is for new topically applied drugs, which would penetrate the cornea efficiently, provide lasting efficacy (that is, not induce pharmacological adaptation), and produce minimal and acceptable systemic or ocular side effects. Ideally, a drug or prodrug should not undergo undesirable metabolic changes before reaching its specific cellular receptor target site, and it should bind to that site with high affinity. Also, drugs should be sought to stimulate aqueous humor production for the medical treatment of hypotony prior to surgery for chorioretinal detachment.

During inflammation, many pharmacologically active substances are released, some of which may adversely affect the eye. Because these agents may contribute to the genesis of glaucoma secondary to uveitis, preventing their release or neutralizing their effects are important pharmacologic and immunologic goals. Earlier studies showed that different compounds are released following different types of insults or trauma to the eye. These substances frequently affect the composition of aqueous humor, or its rate of inflow, which in turn induces changes in intraocular pressure. To develop effective medical treatments, it is important to understand the mechanisms underlying the effects of these agents on aqueous inflow. It may be possible to stimulate the transport processes by which prostaglandins and other irritative compounds are removed from the intraocular tissues, and specific antagonists of the agents involved in ocular inflammatory reactions should be evaluated as a basis for developing treatments for uveitis and other inflammatory conditions and for preventing the secondary glaucomas they cause.

Carbonic anhydrase inhibitors reduce aqueous humor inflow. However, present agents must be administered orally. Because their use is frequently accompanied by unacceptable side effects, compliance with therapy is often poor. An effective, topically applied carbonic anhydrase inhibitor, which would be effective at lower dosages and diminish such side effects, would greatly improve patient use of these drugs. Because inhibition of the ATPase of the ciliary epithelium can lead to a decrease in the rate of aqueous humor inflow, topically effective ATPase inhibitors should be sought and tested for possible use in treating glaucoma. Some recently isolated water-soluble marihuana-derived compounds also inhibit aqueous humor inflow in laboratory animals; their mechanisms of action and their clinical potential remain to be evaluated. These three types of inhibitors of aqueous humor are not tissue specific, and careful research will be required to assure that they do not produce side effects or adversely influence enzymes and transport processes located in other regions of the eye.

Because the aqueous humor is the source of nutrients and oxygen for the lens and it bathes anterior uveal tissues and the corneal endothelium, the effects of chronic low aqueous flow rates on the biochemical status of these tissues must be evaluated, because a minimum flow rate may be essential for their physiological and biochemical integrity. For example, ascorbate levels in aqueous humor are lowered following administration of vanadate, implying an effect on blood flow through the ciliary body. The effects of diminished blood flow should be examined in more detail, to determine if it is detrimental; also, alterations in aqueous ascorbate levels may affect other anterior uveal tissues.

The effects of hormones such as epinephrine, vasopressins, or steroids on the regulation of aqueous inflow are still uncertain. Although an apparent correlation has been shown between diurnal changes in levels of plasma glucocorticoids and intraocular pressure, a direct role for steroids in the regulation of intraocular pressure has not been proved. A link has been demonstrated between vasopressin levels and aqueous inflow rate (and intraocular pressure) in rabbits,[96] but such a connection has not been established in man.

Experimental evidence has long indicated a central nervous system effect on intraocular pressure, but a central regulatory mechanism has not been defined in man. For example, injections into the rabbit third ventricle of prostaglandins, arachidonic acid, and hypoosmotic solutions all increase intraoc-

ular pressure by increasing aqueous humor inflow.[97] Intraventricular injection of calcium ions causes a dose-dependent elevation of intraocular pressure and a reduction in body temperature.[98] Also, hypothermia decreases[99] and hyperthermia increases[100] aqueous formation, and general anesthetics such as halothane,[101] barbiturates, and ketamine[102] affect intraocular pressure, again suggesting the existence of a central control mechanism for aqueous humor formation. Some studies have suggested that optic nerve section influences ocular responses such as those caused by osmotic stress or barbiturates,[103] but not the rise in intraocular pressure caused by hyperthermia.[100] Further elaboration of these observations could provide important information about the role of the central nervous system in aqueous humor formation. It is not known if the cannabinoids act upon neural pathways to affect aqueous humor formation or if the effect is humoral or local. The importance of the central nervous system in regulating aqueous humor inflow should be evaluated in more detail to provide information about the extent, mechanisms, and the pathways of control. Such knowledge may open new avenues for therapy.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Aqueous Humor Dynamics: Inflow," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

### *Program Base*

- Study the biophysics and biochemistry of fluid exchange, flow, and transport in the anterior chamber.
- Study the cellular mechanisms of drug action to alter rate of inflow of aqueous humor.
- Conduct studies of the preclinical pharmacology of new drugs that reduce aqueous humor inflow.
- Study the physiology and pathophysiology of aqueous humor inflow in various types of glaucoma (and hypotony).
- Study the ultrastructure and cell biology of tissues involved in aqueous humor formation.
- Conduct studies to improve present therapeutic measures.

### *Program Development Priorities*

- Apply new methods to studies of the physiology and pharmacology of fluid movement in the ciliary body of primates and humans.
- Investigate endogenous neural and humoral regulating mechanisms. Especially, use new technology and findings in cell biology and transport physiology, which show promise of leading to improved therapy.
- Develop new noninvasive methods of measuring aqueous humor production.
- Develop and test under clinical conditions new medical methods to control aqueous humor production.

# RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## PRIMARY OPEN-ANGLE GLAUCOMA

AQUEOUS HUMOR DYNAMICS: INFLOW

| | No. of Grants FY 1981 | Panel Recommendation FY 83 Add. Grants | Panel Recommendation FY 83 Total Grants |
|---|---|---|---|
| **Program Base** | | | |
| A. Study the biophysics and biochemistry of fluid exchange, flow, and transport. | 6 | −1 | 5 |
| B. Study cellular mechanisms of drug action to alter rate of fluid inflow. | 6 | 0 | 6 |
| C. Conduct studies of the preclinical pharmacology of new drugs that reduce inflow. | 6 | −1 | 5 |
| D. Study how inflow processes differ in various types of glaucoma and in hypotony. | 1 | 0 | 1 |
| E. Study the ultrastructure and cell biology of tissues involved in aqueous humor formation. | 1 | 0 | 1 |
| F. Conduct studies to improve present therapeutic measures. | 1 | 0 | 1 |
| **Program Development Priorities** | | | |
| A. Apply new methods to studies of the physiology and pharmacology of fluid movement in ciliary body. | 2 | 4 | 6 |
| B. Investigate endogenous neural and humoral regulating mechanisms. | 3 | 1 | 4 |
| C. Develop new noninvasive methods of measuring aqueous humor production. | 0 | 2 | 2 |
| D. Develop and test under clinical conditions new medical methods to control aqueous humor production. | 1 | 2 | 3 |
| **Subtotal Grants** | **27** | **7** | **34** |
| **(% of Program)** | **(30)** | **(20)** | **(27)** |
| **Total Estimated Cost** | **$2,885,000** | **$1,059,000** | **$3,944,000** |

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# 3

# AQUEOUS HUMOR DYNAMICS: OUTFLOW

## INTRODUCTION

*GLAUCOMA IS A DISEASE* in which the intraocular pressure is too high for an individual's normal optic nerve structure and function to be maintained. Understanding the physiologic and anatomic bases for the control of normal intraocular pressure, how they are abnormal in glaucoma, and how they can be altered therapeutically are essential prerequisites for improving treatment of this disease.

The anterior chamber angle tissues, between the peripheral cornea and the iris insertion at the ciliary body, through which aqueous humor leaves the eye, offer a certain normal resistance to fluid outflow. In response to the inflow of aqueous humor, intraocular pressure builds up to a steady-state level sufficient to force fluid across that resistance at the same rate at which it is produced by the ciliary body. In the eye of a person with glaucoma, this resistance is unusually high, causing an elevated level of intraocular pressure. An understanding of the factors governing normal outflow resistance and ways of manipulating them is vital to understanding and treating glaucoma.

Figures 1 and 2 schematically illustrate the basic anatomy of the anterior chamber angle and the normal flow pathways of aqueous humor. Aqueous humor formed in the ciliary processes enters the posterior chamber, flows around the lens and through the pupil, and leaves the eye by way of two pathways at the anterior chamber angle: (1) through the trabecular meshwork, across the inner wall of Schlemm's canal, into collector channels, aqueous veins, and the general venous circulation—the trabecular or conventional route; and (2) through the anterior face of the ciliary muscle, through the connective tissue between muscle bundles, into the suprachoroidal space, and out through the sclera—the posterior (unconventional or uveoscleral) route.[1]

Aqueous humor leaves the anterior chamber by way of conventional and unconventional routes and by passive bulk flow. This physical process and its modulation by physiologic and pharmacologic stimuli are governed by the gross and ultrastructural anatomy of the chamber angle in both the normal eye and in glaucoma. Therefore, to prevent, treat, or cure glaucoma, a comprehensive understanding is needed of the chamber angle anatomy, factors that affect the cells of the angle tissues and their extracellular products, and the associated biomechanics of fluid movement across the chamber angle tissues.

Administration of a large number of drugs, hormones, transmitters, and peptides improves aqueous humor outflow; such agents are used to treat glaucoma. An example is the classic miotic, pilocarpine, the use of which remains at the forefront of glaucoma therapy. However, the "pharmacological profile" of the chamber angle tissues and their responses to drugs is far from complete, and much is still to be learned about the sensitivity and specificity of the receptors of the outflow pathways to pharmacologic agents.

Correlating the pharmacological profile of the chamber angle tissues with alterations in biomechanics of fluid flow skips the intervening biochemical and cellular events by which the tissues translate the pharmacological stimulus into improved outflow of aqueous humor. Clarification of these events is vital to understanding the normal and abnormal functioning of the filtration angle tissues and to development of new types of treatment. Normally there may be some hormonal or neural control over aqueous humor outflow. Identification of such mechanisms

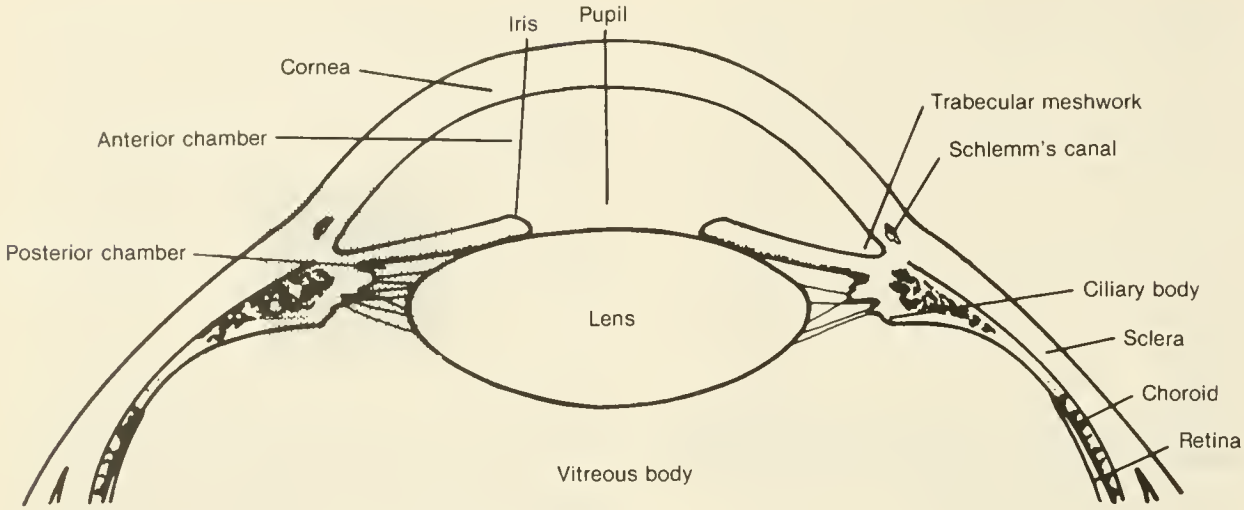


FIGURE 1. Cross sectional representation of the anterior chamber of the eye. The angle is shown in the shaded area.

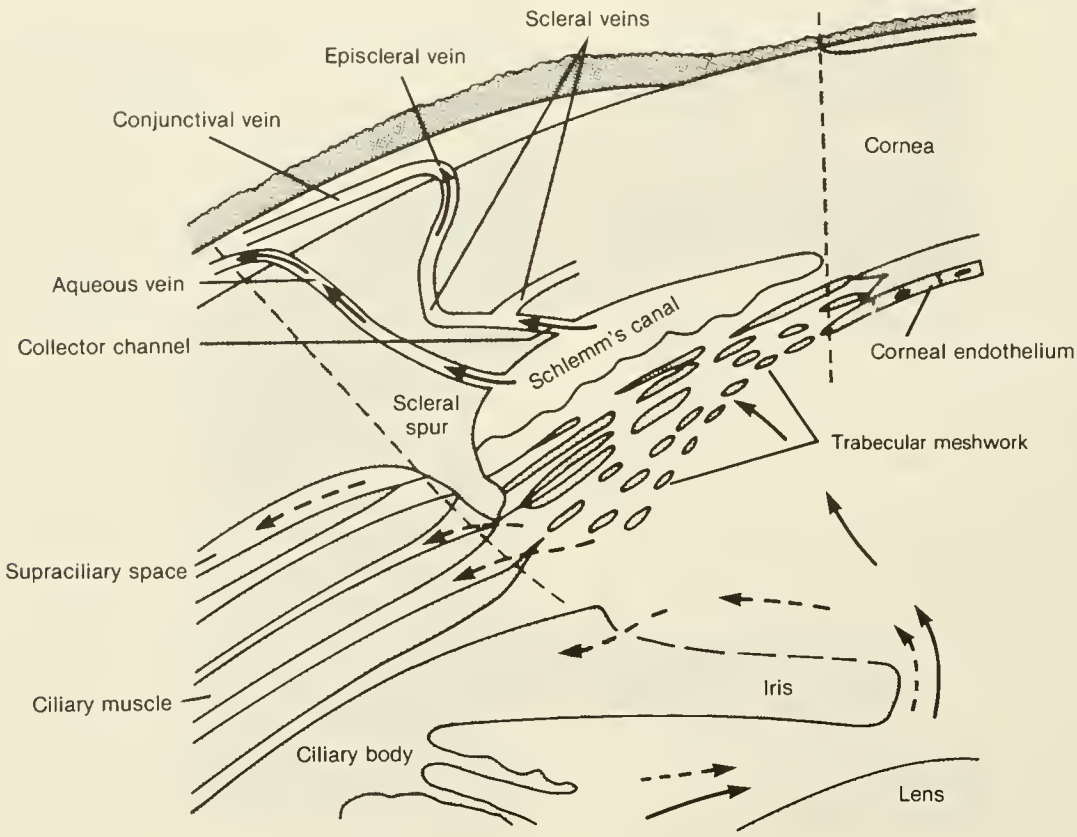


FIGURE 2. An expanded schematic presentation of the structures of the anterior chamber angle. The limbus is demarcated by interrupted lines, the conventional flow of aqueous humor by arrows and the unconventional by crossed arrows. (Modified and reproduced with permission from Svedbergh B: Aspects of the aqueous humor drainage: Functional ultrastructure of Schlemm's canal, the trabecular meshwork and the corneal endothelium at different intraocular pressures. *Acta Universitatis Upsaliensis* 256, 1976.)

would aid in understanding the biology of the outflow pathways and might provide another approach to their functional manipulation.

For many years, the trabecular meshwork was viewed as a "black box," and its structural and functional properties and responses to drugs were attributed to the meshwork as a whole. Recent technical advances in electron microscopy, physiology, pharmacology, biochemistry, cell biology, and tissue culture have made it possible to focus directly on the details of the biology of the cells of the trabecular meshwork and Schlemm's canal. This has provided insights into normal and pathologic states, increased understanding of responses to antiglaucoma drugs, and laid the groundwork for new investigations into normal and abnormal trabecular function and for possible drug therapy. Careful application of these techniques, especially in the areas of cell biology and tissue culture, should help solve many of the problems of aqueous humor outflow.

When medical treatment of glaucoma does not sufficiently control elevated intraocular pressure, surgery becomes necessary. Surgery to improve aqueous humor outflow either employs microsurgical methods to cut through the diseased meshwork (trabeculotomy), uses a laser to stretch the meshwork (trabeculoplasty), creates a new channel for aqueous humor outflow ("filtering operation"), or alters the fluid flow pathways within the eye (cyclodialysis). None of these procedures is perfect; in about 15 percent of patients control of the pressure is not successful or complications occur. The pathophysiologic mechanisms governing success, failure, and complications of these operations are not well understood, and methods must be developed to increase their success.

# SUBPROGRAM OBJECTIVES

- To define the biomechanics of aqueous humor outflow in the eyes of normal persons and people with glaucoma.
- To define the biology and pharmacology of the aqueous humor outflow pathways at the cellular, tissue, and organ levels in normal eyes and eyes with glaucoma, and to determine how the properties of these sites are modified by treatment.
- To develop and test new ways to improve aqueous humor outflow in glaucoma.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

Twenty-four grants supported by the National Eye Institute in FY 1981 at a total cost of $2,273,000 were mainly devoted to studies of aqueous humor outflow. Several laboratories are studying the ultrastructure of the aqueous humor outflow pathways. In vitro studies, using a variety of techniques including electron microscopy, histochemistry, and methods for enzyme localization, are attempting to define the normal cellular and extracellular structures and materials in the trabecular meshwork and Schlemm's canal; the effects of pharmacological and chemical agents and of aging are being studied, and structural-functional correlations sought. Eyes of animals (including primates) and those from normal persons and glaucoma patients are being studied.

Other laboratories are assessing the pharmacologic and physiologic effects of drugs on intraocular pressure and outflow resistance in humans and in animals (including monkeys) to form response profiles of the outflow tissues and their regulatory mechanisms. Some laboratories are attempting to correlate physiologic and pharmacologic responses to drugs with structural alterations of the chamber angle, an approach that has great potential for providing new insights into the mechanisms governing aqueous humor outflow.

Pharmacologic, biochemical, and metabolic studies on freshly dissected angle tissues are being pursued, despite the minute amounts of material available from the outflow pathways. Cell culture techniques offer an opportunity to obtain single types of cells in quantities sufficient for such investigations. Correlations of data obtained using cultured cells with findings obtained in pharmacophysiologic experiments should greatly enhance understanding of the biology of the trabecular meshwork.

Surgical techniques are being developed and refined. Investigators are evaluating the application of laser energy to the trabecular meshwork in the clinic and in the laboratory as a "noninvasive" surgical means of decreasing outflow resistance. The effects of aqueous humor factors on wound healing are being examined in hope of improving the success rate of fistulizing procedures.

In summary, the National Eye Institute supports a large and diverse program of clinical and laboratory research projects and some investigator training and career development awards for studies of aqueous humor outflow. This is appropriate in view of the importance of this area to glaucoma research in general.

# RECENT ACCOMPLISHMENTS

## *Physiology, Pharmacology, and Biochemistry*

Advances have been made in defining the physiologic responses of the outflow pathways to therapeutic agents. Much of this research has centered on cholinergic and adrenergic drugs, because they are currently the mainstays of glaucoma treatment.

Pilocarpine, the cholinergic drug most frequently used to treat glaucoma, reduces outflow resistance by causing ciliary muscle traction on the trabecular meshwork, rather than by constricting the pupillary sphincter or acting directly on the meshwork.[2–4] Continuous stimulation of the anterior segment with high levels of cholinergic agonists induces marked subsensitivity of pupillary, accommodative, and outflow resistance responses to these drugs.[5–12] Subsensitivity is associated with a decrease in the number of high-affinity and possibly low-affinity muscarinic cholinergic receptors.[13–16] This is consistent with the concepts that tissue sensitivity to cholinergic drugs is inversely related to the average local concentration of agonist, and that agonist concentration regulates the tissue receptor number or density by way of a negative feedback mechanism.[7,8] However, other factors appear to affect ocular sensitivity to cholinergic drugs. Recent histological and ultrastructural studies of monkey eyes have provided evidence that tissue damage to the trabecular meshwork, iris sphincter, ciliary muscle, and ciliary epithelium occurs with long-term cholinergic treatment.[17,18] This damage may also contribute to the loss of tissue sensitivity with cholinergic drug therapy, and suggests that some antiglaucoma medications themselves may produce effects toxic to the aqueous humor production and drainage apparatus.

Various adrenergic agonists also may decrease outflow resistance. Adrenergic effects on outflow resistance are not related to actions on the iris or ciliary muscle but are probably mediated by a direct action on the cells of the trabecular meshwork or inner wall of Schlemm's canal,[19,20] a process probably involving the adenylate cyclase-cAMP system.[21–25] Adrenergic agonists and antagonists also may affect aqueous humor outflow by acting on the intrascleral and extrascleral vasculature.[26] Treatment with adrenergic agents can modify adrenergic receptors and nerve endings and thus affect tissue sensitivity to these drugs.[27–30] Also, adrenergic and cholinergic systems possibly may interact and modulate each other's effects on tissues of the anterior segment.[31] The clinical significance of these relationships remains to be determined.

The epinephrine prodrug, dipivalyl epinephrine, which penetrates the eye nearly 20 times more readily than epinephrine itself, is converted to epinephrine by esterases within the anterior segment.[32] Dipivalyl epinephrine is therapeutic at a much lower dosage[33] than epinephrine; thus, it significantly reduces the risk of some ocular and systemic side effects associated with topically administered epinephrine.[34]

Various prostaglandins may increase or decrease IOP and perhaps outflow resistance in animal eyes,[35–38] but their various effects on vascular permeability and smooth muscle make it difficult to determine their sites and mechanisms of action. Some cannabinoids and aqueous extracts of cannabis leaf lower intraocular pressure in man and certain animals.[39–42] There is evidence that these drugs affect both inflow and outflow of aqueous humor,[40–42] but the work on outflow has been primarily in rodents, and there is need for careful investigation to determine how they affect the aqueous humor outflow system in primates and man.

The posterior (unconventional) drainage routes may be more complex than originally thought, with aqueous humor leaving the eye by way of the vortex veins as well as directly through the sclera.[43] Fluorophotometric measurements of aqueous humor flow combined with tonography in living animals and in humans have shown that drug effects on posterior drainage can be estimated noninvasively.[44,45] Further characterization of the physiology and pharmacology of posterior drainage mechanisms may lead to new types of treatment for glaucoma. Acute or chronic hypotony secondary to ocular disease or surgery can itself have serious ocular consequences. Recent studies of experimental hypotony associated with iatrogenic ciliochoroidal detachments in monkeys point to a potential pathophysiologic role for the posterior outflow pathways.[46]

The biochemistry and metabolism of the trabecular meshwork have long been obscure. Studies are now defining the enzymatic pathways and metabolic requirements of excised bovine trabecular meshwork.[47] Glucocorticoid-sensitive target cells in the outflow tissues of the rabbit and in human trabecular tissue have been identified by radioautographic studies.[48] Further studies of normal human tissues in tissue culture, especially tissues from individuals whose intraocular pressure rises in response to administered glucocorticoids, are needed to evaluate the clinical significance of this finding. Endogenous hormonal and neural mechanisms may be important regulators of aqueous outflow,[49,50] but knowledge of many essential details is lacking.

## *Anatomy and Cell Biology*

Morphologic studies are essential to understanding potential changes in the outflow pathways associat-

ed with normal aging and disease. Examination of normal tissues by thin section and freeze-fracture electron microscopy indicates that the intercellular spaces between trabecular endothelial cells are open, whereas tight junctions between the endothelial cells of the inner wall of Schlemm's canal represent a barrier to the outflow of aqueous humor.[51] Using the technique of S-1 myosin decoration, investigators have shown that actin filaments, the contractile elements of cells, exist in human and monkey endothelial cells in the trabecular meshwork and in Schlemm's canal.[52,53] In other studies, intracamerally administered cytochalasin B and the chelators EDTA and EGTA caused a marked decrease in outflow resistance in monkey eyes due to disruption of the trabecular meshwork and inner canal wall.[54-58] Taken collectively, these studies demonstrate that cytoskeletal components, cell junctions, and contractile proteins play an important role in maintaining, and possibly regulating, tissue architecture and outflow resistance in the trabecular meshwork and Schlemm's canal. The possibility of manipulating these systems to therapeutic advantage is intriguing.[59]

Extracellular materials normally in the trabecular meshwork may be important in the regulation of outflow resistance. Abnormal types or amounts of some of these substances may clog the meshwork in some types of glaucoma. A wide variety of extracellular macromolecules, including hyaluronic acid and other glycosaminoglycans, collagen, fibronectin and other glycoproteins, are produced by cells of the trabecular meshwork. The exact natures and roles of these materials need to be defined. For instance, "washout" of extracellular material may account for the progressive decrease in outflow resistance occurring during perfusion of the anterior chamber.[60-69] Trabecular endothelial cells also have phagocytic capabilities[70-73] which may be important in maintaining normal trabecular function.[74]

Identification of pathological changes in the trabecular meshwork specifically associated with the development of glaucoma has proved difficult. There is evidence that in glaucoma partially characterized electron-dense material collects in the cribriform region of the meshwork.[75] Also, the number of cells in the trabecular meshwork decreases with age in the normal population; this may be accelerated in glaucoma.[76]

Trabeculectomized monkey eyes have ultrastructural abnormalities in the unoperated portion of the meshwork several months after surgery, perhaps due to underperfusion of the remaining meshwork.[77] Also, monkeys treated chronically with acetazolamide have abnormalities in their trabecular meshwork,[18] suggesting that long-term reduction of the rate of aqueous humor formation with these agents may not be as innocuous as generally thought. Alteration of the chemical composition of the aqueous humor by drugs or surgery may also affect the properties of the meshwork. This may be analagous to experimental perfusion of the monkey anterior chamber which causes a decrease in outflow resistance.[69,78,79]

Some progress has been made in defining the anatomic and biomechanical relationships of the inner and outer walls of Schlemm's canal (including causes and effects of canal collapse), the trabecular meshwork, and the intrascleral and extrascleral collector channels, and their possible effects on aqueous humor outflow.[80-90]

A major advance in glaucoma research is the recent success in applying cell and organ culture techniques to human and monkey trabecular endothelium (see Chapter 1, "Etiology, Epidemiology, Management, and Therapy"). Several laboratories have shown that it is possible to induce trabecular cells to divide in vitro.[91-94] These cells can serve as a potentially useful tool for controlled experimental studies, because certain cultures can be propagated for three to four passages while retaining their distinctive in vivo morphological characteristics[67] and possessing glucocorticoid and adrenergic receptors.[95-97] In the future, cultured human trabecular cells may provide much new information about the physiologic, pharmacologic, biochemical, and morphologic properties and responses of normal trabecular cells and those from eyes with glaucoma; however, potential changes due to the cell culture environment itself and "in vitro aging" must be evaluated.[98]

## *Surgery*

The usual surgical treatment to improve outflow of aqueous humor is to create a fistula between the anterior chamber and the subconjunctival space. Various subscleral fistulizing procedures (usually inappropriately called "trabeculectomy") have come into widespread use over the past decade and are thought to be safer than the previously popular full-thickness procedures.[99] In selected desperate situations, insertion of a plastic one-way valve connecting the anterior chamber and the subconjunctival space may be beneficial.[100] The failure of fistulizing procedures usually results from scarring of conjunctival and episcleral tissues over the fistula site, and preliminary studies suggest that chemical factors in the draining aqueous humor may contribute to this response.[101,102] Trabeculoplasty, the treatment of the trabecular meshwork with energy from an argon laser, is coming into increasing use to improve outflow of aqueous humor.[103-106] It appears that the multiple laser burns applied to the meshwork form scars that exert tension upon the meshwork to open drainage pathways into Schlemm's canal. The prospect of an essentially

noninvasive one-time treatment for improving aqueous humor outflow is exciting, but many questions remain to be answered concerning long-term efficacy and safety, patient selection, and optimal treatment techniques. For example, caution must be observed because very extensive laser treatment of the trabecular meshwork in monkeys increases outflow resistance and raises intraocular pressure.[107]

# RESEARCH NEEDS AND OPPORTUNITIES

In reviewing research progress in aqueous humor dynamics since publication of the 1977 National Advisory Eye Council program planning report,[108] it is apparent that the previously published recommendations had the desired effect of stimulating studies that were identified as important and attainable. Additional projects are desirable in these areas, especially those employing new techniques directed at solving the problems discussed in the following paragraphs.

Further characterization of the biology of the trabecular meshwork should be undertaken on several different levels. Responses of outflow resistance to various categories of drugs should be defined, using selective agonists, antagonists, and mediators of cellular responses. Morphological correlates of these physiological responses should be identified, using modern ultrastructural and histochemical techniques. Further development and application of tissue culture technology should encourage more specifically targeted pharmacological, biochemical, and morphological studies of trabecular endothelial cells. Correlations of responses of cells in tissue culture with in vivo data should provide major new insights into the basic biology of the trabecular meshwork and mechanisms and sites of drug effects.

Physiologic and pharmacologic influences on aqueous humor outflow need to be studied with respect to the specific target tissue(s) affected—including iris, ciliary muscle, trabecular meshwork and Schlemm's canal, intrascleral and extrascleral vasculature—and to the additive and competitive effects of different classes of drugs. Results of such studies should be interpreted in parallel with in vitro studies of receptor-response profiles performed on excised tissue pieces or cultured cells. The biochemical links should be sought between the cellular response, such as receptor binding, protein and glycosaminoglycan synthesis, or metabolic changes, and the related physiological effect, such as increased or decreased outflow resistance, to determine how the biological phenomenon produces the physical phenomenon.

The roles of extracellular substances—macromolecules in particular—in determining the outflow resistance still need to be defined. The cellular sources of specific macromolecules in the outflow pathway and the processes controlling their production should be defined. The role of aqueous humor components in regulating levels of metabolic activity of the trabecular cells needs to be explored. These studies must be conducted and interpreted with the knowledge that the normal trabecular meshwork is constantly perfused with aqueous humor; thus, more information is needed about how the composition of aqueous humor may affect the biological responses of meshwork tissue.

There are many unanswered questions about the distribution and amount of resistance in the outflow pathways and the manner of fluid flow through the meshwork, juxtacanalicular connective tissue layer, cellular layer of the inner wall of Schlemm's canal, Schlemm's canal itself, collector channels, and vascular beds into which the collector channels empty. The biomechanics of the drainage areas should be investigated thoroughly to determine how they are affected by the intraocular pressure and by pharmacologic influences.

The benefit that can accrue from an improved drug design or delivery system is illustrated by the improvement in the therapy of glaucoma attained by substituting dipivalyl epinephrine for epinephrine. Similar opportunities to improve drug delivery may exist for other therapeutic agents, either by changing the formulations or the structures of effective drugs.

The effects of laser energy on the trabecular meshwork need to be evaluated in the treatment of glaucoma and in the laboratory at the structural and ultrastructural, physiologic, biochemical, and cellular levels. The physiologic factors governing success, and the pathologic processes determining failure or the complications of conventional fistulizing surgery must be defined more thoroughly. Also needed are further studies of surgical methods used to relieve elevated intraocular pressure by enlarging or creating new pathways for the outflow of aqueous humor. For example, laboratory studies to clarify the process by which conjunctival fibroblasts form scar tissue and seal fistulas, causing filtering operations to fail, may lead to improving the success of this procedure. We need to determine why filtration surgery fails in certain black patients and patients with some types of secondary glaucoma or aphakia. Is failure of filtration surgery in some patients with aphakia or with ocular inflammation due to altered composition of aqueous humor? These and many other questions that haunt everyday ophthalmic practice may be answered by appropriately designed controlled clinical trials.

The unconventional routes of aqueous humor outflow have not been studied as thoroughly as they

should be. Understanding these routes of fluid drainage may lead to new therapeutic methods which would increase aqueous humor outflow through the scleral outflow pathway or by way of a choroidal absorption mechanism.

One problem with much past research on outflow mechanisms is that it has been conducted without sufficient interaction among investigators using different approaches. Structured interdisciplinary collaboration among laboratories should be encouraged, whether by consultative arrangements, joint projects and grants, or other mechanisms.

Specific areas ripe for multidisciplinary investigation include studies of: outflow biomechanics; the ocular pharmacology and toxicology of cholinergic and adrenergic drugs, corticosteroids, cannabinoids, cytochalasins, chelators, prostaglandins, and carbonic anhydrase inhibitors; the properties of cells of the outflow pathways including their shape, structure, and motility; the properties of extracellular materials (such as glycosaminoglycans) in the trabecular meshwork; posterior outflow; the effects of laser trabeculoplasty; and the pathophysiology of fistulization and hypotony.

Collaborative consultation with engineers and physicists should also be encouraged to develop noninvasive methods (preferably not requiring contact or anesthesia) to measure intraocular pressure, outflow resistance, and their underlying mechanisms without disturbing the underlying physiology.

Of necessity, much of this work must be conducted in normal animals. Especially encouraged are studies conducted in monkeys, because research in primates can yield insights into the basic biology of the outflow pathways directly applicable to the pathophysiology of glaucoma and the development of new therapies.

Because it is important to know what goes wrong in the trabecular meshwork to obstruct outflow of aqueous humor and cause glaucoma, an animal model truly comparable to human ocular hypertension or primary open-angle glaucoma would be invaluable. However, presently available animal models of elevated intraocular pressure (monkeys with very extensive treatment of the meshwork [107] and rabbits receiving intracameral alpha-chymotrypsin [109]) have pathological features that are not characteristic of human glaucoma. Animals with naturally occurring glaucoma (such as the beagle [110] and the buphthalmic rabbit, [111,112]) also have drawbacks in that the animals have associated genetically transmitted deficiencies and anatomic differences from man. The animal models also progress to secondary angle-closure glaucoma, which does not occur in human primary open-angle glaucoma.

Cultured human trabecular meshwork cells should be a valuable tool for understanding pathogenetic mechanisms in the outflow pathways, but studies using material from primary open-angle glaucoma patients will need exceptionally rigorous controls to help distinguish glaucoma-related changes from those due to drug effects, age, or other secondary alterations in the cells. Also, the underlying mechanism needs to be determined separately for each type of glaucoma.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Aqueous Humor Dynamics: Outflow," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

## *Program Base*

- Investigate the cell biology of the outflow tissues and the relevant cells from normal and diseased eyes in culture and correlate the resultant information with in vivo observations of human and primate eyes.
- Investigate the structure and ultrastructure of the aqueous humor outflow system in eyes of normal and aged individuals and of glaucoma patients.
- Determine drug effects on the outflow of aqueous humor and intraocular pressure.
- Study the biomechanics of normal and abnormal aqueous humor outflow.

- Pursue other studies of the normal and abnormal outflow system, including use and development of models of glaucoma.

### *Program Development Priorities*

- Develop new noninvasive techniques to study normal and abnormal aqueous humor outflow.
- Devise methods to study posterior (uveal) outflow pathways and the influence of aqueous humor composition on outflow.
- Characterize the molecular, biological, and physiological effects of drugs on the target tissues of the outflow apparatus and their physiologic correlates.
- Study the basic mechanisms involved in the failure of filtration surgery and the role of aqueous humor factors in wound healing.
- Conduct controlled clinical trials of laser trabeculoplasty.

## RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## PRIMARY OPEN-ANGLE GLAUCOMA

AQUEOUS HUMOR DYNAMICS: OUTFLOW

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Investigate cell biology of outflow tissues in culture and correlate with in vivo observations in human and primate eyes. | 7 | 0 | 7 |
| B. Investigate the morphologic basis of outflow system. | 1 | 0 | 1 |
| C. Determine drug effects on the outflow of aqueous humor and intraocular pressure. | 4 | 0 | 4 |
| D. Study the biomechanics of normal and abnormal aqueous humor outflow. | 2 | 0 | 2 |
| E. Pursue other studies of the normal and abnormal outflow system. | 5 | −3 | 2 |
| **Program Development Priorities** | | | |
| A. Develop noninvasive techniques to study normal and abnormal aqueous humor outflow. | 0 | 2 | 2 |
| B. Study posterior (uveal) outflow pathways and influence of aqueous humor composition on outflow. | 1 | 1 | 2 |
| C. Characterize effects of drugs on target tissues of outflow apparatus and their physiologic correlates. | 4 | 3 | 7 |
| D. Study the basic mechanisms in failure of filtration surgery and the role of aqueous humor factors in wound healing. | 0 | 1 | 1 |
| E. Conduct controlled clinical trials of laser trabeculoplasty. | 0 | 3 | 3 |
| **Subtotal Grants** | **24** | **7** | **31** |
| **(% of Program)** | **(27)** | **(20)** | **(25)** |
| **Total Estimated Cost** | **$2,273,000** | **$1,323,000** | **$3,596,000** |

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# 4

# THE OPTIC NERVE

## INTRODUCTION

*VISUAL LOSS IN* glaucoma, either partial or total, results from actual destruction of axons in the optic nerve, the damage typically occurring in chronic glaucoma over a course of months and years. Damage to the optic nerve is a consequence of the pathological course of glaucoma and is generally assumed to be due to an elevated or individually intolerable level of intraocular pressure. How this damage is caused is still a matter under investigation. The two major theories hold that pressure induces either ischemia or mechanical effects that initiate nerve damage.

The optic nerve consists of the axons of the retinal ganglion cells and glial and vascular supporting elements. The ganglion cell bodies and the portion of the ganglion cell axons that lie within the eye receive their blood supply from the intraocular branches of the central retinal artery. The ganglion cell axons come together at the optic nerve head, where they pass through fenestrations in an area of the scleral wall, known as the lamina cribrosa, to leave the eye as the optic nerve. While passing through the lamina cribrosa, the ganglion cell axons are supplied by branches of the short posterior ciliary arteries, and for a short distance just anterior and posterior to the lamina cribrosa the axons are supplied from branches from the peripapillary choroid. In the intraorbital optic nerve, the ganglion cell axons are again supplied by branches of the central retinal artery (Figure).

For many decades, the "ischemic" theory, suggesting that elevated intraocular pressure somehow interferes with blood flow in the optic nerve head, was the principal explanation for nerve damage in glaucoma. The anatomy of the blood vessels of the optic nerve was studied in detail, and hypotheses were proposed to explain how even mildly elevated intraocular pressure might affect the blood flow in the optic nerve head (perhaps by shunting the blood into other vascular beds) without affecting blood flow in or significantly damaging the adjacent retinal and choroidal tissues or any other intraocular structures.

Fluorescein angiographic studies of human eyes suggests that in glaucoma vascularity is reduced in the optic disc but not in the other portions of the optic nerve which are supplied by the central retinal artery.[1] Decreased perfusion in the vessels supplying the anterior portion of the optic nerve could be caused by a rise in the intraocular pressure, a fall in the blood pressure in the involved vessels, or increased resistance to blood flow caused by intrinsic vascular disease. Supporting this concept is the optic disc excavation and pallor typical of the glaucoma which is seen in the the absence of elevated intraocular pressure in patients with sectoral anterior ischemic optic neuropathy,[2] in patients giving a history of severe shock episodes,[3] and in patients with splinter hemorrhages on the optic disc.[4,5]

Various physiologic methods have been employed in attempts to measure blood flow in the optic nerve.[6,7] However, the area of the optic nerve that is affected in glaucoma is small and inaccessible to observation, so that the quality of the information obtained has been variable and uncertain, in contrast to the reliable information that can be obtained about the circulation in the retina and uveal tract. For example, the autoregulatory characteristics of the retinal circulation can be quite well defined. Such physiologic studies are important, but additional approaches are required to determine if the effect of an experimentally induced acute pressure rise in intraocular pressure is different from that which occurs naturally in chronic glaucoma. It is not known, for example, if the sequence of events observed in experimental animals is exactly the same

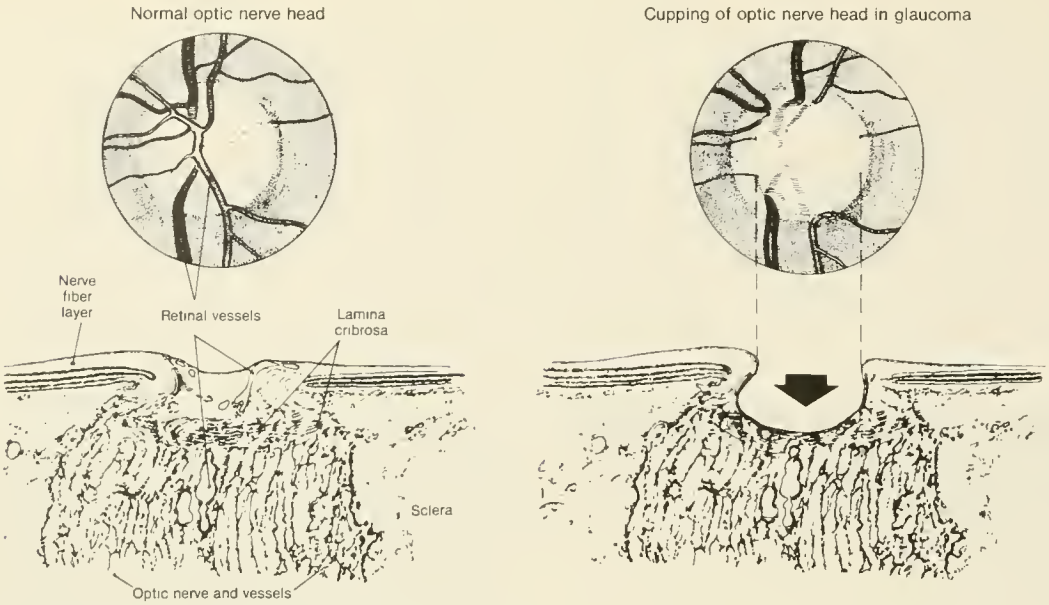


FIGURE. The appearance of the optic nerve head in the normal eye and in glaucoma, showing the cupping or excavation typical of glaucoma.

as in humans; nor why low levels of intraocular pressure affect blood flow in some individuals but not others; nor why laboratory animals are not affected at low pressure levels.

An alternative theory is that increased intraocular pressure may damage the optic nerve by mechanical compression of the axons in the lamina cribrosa region.[8] It is now known that axonal transport, which is a vital physiologic function of nerves, is blocked at the optic nerve head when intraocular pressure is experimentally increased.[9,10] Because axonal transport is an active metabolic process, its blockage could be the logical result of impaired blood flow. However, the fact that axonal transport can be blocked when a nerve is pinched or constricted has reawakened interest in the mechanical compression theory. In the optic nerve, axonal flow might be hindered by pressure forcing the axons against the rigid walls of the holes in the lamina cribrosa through which the nerve fibers leave the eye. Scanning electron microscopy and histologic examinations of eyes from glaucoma patients[11] have shown distortion of the lamina cribrosa and lend weight to the mechanical interpretation. It is not known if distortion of the lamina cribrosa damages the axons by direct mechanical compression or by pinching the blood vessels and producing ischemia, or if distortion is secondary to tissue loss.

The debate between adherents of the vasogenic and mechanical concepts probably cannot be resolved until methods are found to compare the blood supply of the prelaminar, laminar, and retrolaminar portions of the optic nerve in primary open-angle glaucoma patients with that in ocular hypertensives and normal persons, either in life or in fresh eye bank specimens. Studies in primates may suggest new ways to look at human eyes with glaucoma.

Relevant to understanding the mechanisms of nerve damage in glaucoma are studies of the involvement of axonal transport in other ocular conditions such as neuronal necrosis in optic atrophy, regeneration or the failure of regeneration of nerve fibers, and the production of nerve swelling by ischemia or blocked axonal flow (for example, ischemic optic neuropathy and papilledema). Recent advances in general neurobiology should aid understanding of these questions.

Meanwhile, even without understanding the mechanism by which high intraocular pressure induces destruction of the optic nerve, clinical decisions must be made. A major reason for deciding to lower the intraocular pressure therapeutically is the estimated risk of future optic nerve damage and loss of vision if intraocular pressure is not reduced. Epidemiologic studies have shown that few individuals will suffer nerve damage at the mild elevation of pressure typical of most glaucoma patients, and a larger group will be affected at very high levels of pressure.[12]

To avoid treating a large number of people unnecessarily, clinicians must be able to identify those individuals with elevated intraocular pressure who are at risk of optic nerve damage and visual loss. A number of studies have been aimed at finding factors (for example, poor outflow facility, diabetes,

blood factors, hypertension, and family history) that correlate with the occurrence of damage.

A related problem is "low tension glaucoma," in which people lose vision following damage to the optic nerve at levels of intraocular pressure considered to be within the normal range. What determines the difference between such people and those ocular hypertensives who do not have any damage despite elevated intraocular pressure is not known. Individual variations in the susceptibility of optic nerves to different levels of intraocular pressure have not been identified, and a search for statistically significant factors which might determine damage has added little to the ability to predict which eyes are at risk.[13–15] Detailed studies of patients with low tension glaucoma should lead to an understanding of the factors affecting susceptibility to nerve damage in glaucoma.

In the meantime, the best predictor of the future course of the disease in an individual eye is its course in the immediate past; that is, if an eye has already suffered damage at a given level of pressure, damage is likely to progress; if the eye has not suffered damage, there is less likelihood that it will be damaged in the near future. In essence, physicians cannot tell if a person is going to suffer optic nerve damage until they detect changes in the appearance of the nerve head or vision. Therefore, it is important to understand the clinical characteristics of the very earliest stages of optic nerve damage and to find ways to recognize the earliest subtle changes in visual function so that treatment can be initiated before there is any functionally significant degree of visual loss.

The ability to recognize and measure precisely the extent of optic nerve damage and abnormalities of visual function is important for early detection of glaucoma, reaching decisions about starting therapy, and following the progress of patients under treatment. It is especially important that clinicians have the means available to measure accurately signs of continuing deterioration in vision so that therapy can be adjusted accordingly.

# SUBPROGRAM OBJECTIVES

- To understand better the mechanisms by which the optic nerve is damaged by various levels of intraocular pressure in primary open-angle glaucoma and low tension glaucoma and to understand other forms of optic nerve disease.
- To develop better methods of recognizing and quantifying optic nerve damage and loss of visual function.
- To find means of protecting the optic nerve in ocular hypertension and in glaucoma.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981, the NEI supported 16 research grants at a total cost of $1,771,000, which dealt specifically with the functions of the optic nerve related to glaucoma. Among them were grants devoted to laboratory studies of the mechanisms of optic nerve damage, the effects of intraocular pressure on blood flow and axon physiology, and the detailed morphology of the optic nerve head as it may relate to glaucoma. One clinical investigator studied the relationship of blood pressure to the susceptibility of the optic nerve to damage, to determine if ischemia is involved in the mechanism of glaucomatous cupping. Other studies evaluated risk factors for optic nerve damage.

Investigations were directed at clinical evaluation of the optic nerve head by stereoscopic quantification, fluorescein angiography of the optic nerve head, evaluating the visual function in glaucoma, quantifying visual fields, and studying changes in color vision.

Other relevant research was conducted under grants that had a broader scope. For example, grants dealing generally with open-angle glaucoma included projects to detect risk factors, which may provide clues to understanding the mechanism of optic nerve damage. Relevant research also was supported by other agencies or foundations, and some studies were conducted by clinical subspecialists without formal research support.

# RECENT ACCOMPLISHMENTS

That elevated intraocular pressure can interfere with axonal transport in the optic nerve has been shown by several investigators.[16–23] Impaired axonal transport also has been demonstrated in monkeys with chronic glaucoma. These observations provide the clearest evidence of the influence of intraocular pressure on the physiology of the optic nerve head and help to locate the site of pressure-induced damage at the lamina cribrosa. Efforts to relate the damage in the optic nerve to a reduced blood flow have been hampered[24–26] in part by the technical difficulties of measuring blood flow noninvasively in such a small tissue area. Thus,

the question of whether in glaucoma there is reduced blood flow to the optic nerve remains open.[6,7]

Continuing investigation of the anatomy of the lamina cribrosa has revealed regional differences in its structure that correlate with the pattern of nerve fiber damage characteristic of glaucoma.[27-30] The superior and inferior parts of the lamina cribrosa have larger pores and less supporting connective tissue than the remainder of the structure; these are the openings through which pass the arcuate area ganglion cell axons, those most susceptible to damage in glaucoma. Details of nerve fiber anatomy have also been clarified.

In the last ten years, it has become easier to recognize more accurately excavation or cupping (representing a loss of nerve substance and changes in the conformation of the nerve head) of the optic disc early in the stages of glaucoma.[31-34] The task of evaluating the clinical status of the optic nerve is becoming easier as additional signs of early damage are being described and applied to everyday clinical practice.[35-39] Many of the signs correlate with the occurrence of visual field loss.[40,41] However, correlations are not absolute; for example, in some instances a generalized enlargement of the optic nerve excavation occurs in the early stages of glaucoma before there is visual field loss,[42] and in other instances, field loss is detected before excavation of the nerve is recognized. Angiographic studies with fluorescein have shown areas of reduced vascularity in damaged optic nerves, indicating either an underlying ischemic mechanism for optic nerve damage or a secondary vascular loss accompanying the loss of nerve fibers when the optic nerve is damaged.[43-48]

Methods have been devised for quantification of the optic disc configuration by stereophotogrammetry[49,50] and of the vascularity by densitometry[51] and fluorescein angiography. These methods await development into tools that can be used routinely in clinics outside of specialized research institutions. A method of comparing optic nerve configurations recorded at intervals by "stereochronoscopy" has been described, and is under evaluation.[52,53] If this method is validated after multicenter evaluation, and if photographs can be made readily along a standard axis, stereochronoscopy could possibly be utilized in every ophthalmologist's office, since no major equipment other than a fundus camera is required. Statistical methods (discriminant analysis) that have been applied to optic disc features and that can be measured in ordinary clinical examination have shown promise of being useful.[39]

With increased emphasis on early detection and quantification of optic nerve damage and field loss to aid in making therapeutic decisions, the reliability of examinations of the visual field needs to be improved. Unfortunately, there are not many qualified visual field technicians in the United States, and many ophthalmologists are not themselves expert with the technique. Now, several types of automatic and semiautomatic perimeters are available. Some are designed simply to detect defects in the visual field; others can be used to quantify the defects so that serial records may be made of optic nerve status that will enable physicians to detect deleterious changes and adjust their treatments. Careful clinical evaluation of some of these instruments has begun,[54-56] but further evaluations of their potentials and limits are needed.

Recently, several investigators have reported that glaucoma affects aspects of visual function other than the visual threshold, as measured by standard perimetry. In particular, it seems that contrast sensitivity[57,58] and color vision[59] are affected very early in the course of optic nerve damage in glaucoma. At present, the results of contrast sensitivity measurements are not specific enough to indicate their clinical use in assessing glaucoma. It may be beneficial to investigate the relationships to optic nerve damage of aspects of color sensation, temporal summation, VER (visually evoked response in the brain), or other psychophysical aspects of vision.[60] It may be useful also to investigate other tests that may provide earlier detection and better quantification, or be equivalent to the present lengthy visual field examination. This area of research should be fruitful for psychophysicists.

# RESEARCH NEEDS AND OPPORTUNITIES

Current efforts to learn how damage to the optic nerve is correlated with the level of intraocular pressure need to be continued. Only by understanding these mechanism(s) can clinicians hope to recognize which patients with increased intraocular pressure will suffer damage and act to forestall it, and ultimately devise treatments to reduce or reverse damage. At present, the only therapeutic strategy is to lower intraocular pressure; it would be desirable to have a direct treatment to protect the nerve against the damaging effects of pressure. This is especially necessary for patients whose pressure cannot be lowered adequately by medical or surgical treatment and for those with low tension glaucoma.

Studies in animals, especially primates, should continue, with emphasis on overcoming the technical limitations of measuring blood flow in the optic nerve. In addition, biochemical and physiologic aspects of nerve viability such as oxidative metabolism and vascular leakage should be studied, calling

on new findings in neurobiology. Any demonstrable pressure-induced abnormality of the optic nerve (such as blockage of axonal transport) can be used to study the effects of blood pressure and other potentially damaging factors. Although acute experiments can provide valuable information, they do not truly represent chronic open-angle glaucoma. Further attempts should be made to develop a reliable experimental model of chronic glaucoma in which physiologic defects equivalent to those in human glaucoma can be studied.

Other studies should be directed toward understanding the reasons why some nerve fibers are more susceptible to damage than others. It is not known whether susceptibility is related to nerve type (for example, x-cells or y-cells), structural differences in various regions of the lamina cribrosa, or some other factor. As the mechanisms of damage become better understood, research on pharmacologic means to alter the pathophysiologic process is a natural next step.

Other lines of laboratory investigation that may be relevant to glaucoma are studies of hydrocephalus (pressure-induced damage to brain tissue); mechanisms involved in axon degeneration following injury (for example, optic atrophy, spinal cord injury, and peripheral nerve degeneration); processes that allow regeneration of some axons (for example, goldfish optic nerves) but not others; mechanisms of ischemic swelling and damage to axons; and nonischemic mechanisms of swelling or damage to axons (for example, papilledema). Studies of normal neurobiology and the neuropathologic mechanisms of swelling and atrophy in any nerve tissue are intrinsically important and are a basis for understanding optic nerve degeneration in glaucoma.

Because intraocular pressure cannot be manipulated experimentally and the optic nerve cannot be observed directly in man, it will be especially important to study in an appropriate animal model the effects on the optic nerve of the range of pressures encountered in glaucoma.

Efforts should be devoted to developing noninvasive means to study the lamina cribrosa, local blood flow, and other physiologic determinants of optic nerve status to define the naturally occurring pressure-induced effects in human glaucoma. The importance of this information is that humans vary considerably in their sensitivity to pressure-induced damage, as demonstrated by ocular hypertension, low tension glaucoma, and the variable course of glaucoma. Understanding the cause(s) for this variability may provide valuable clues to pathogenetic mechanisms. It is especially important to continue to study the range of pressure-induced changes in human optic nerves in the clinic and in postmortem eyes available to the laboratory. An experimental primate model, which truly represents chronic glaucoma in man, is needed so that the mechanisms of damage in glaucoma can be manipulated and methods for therapy can be tested.

In clinical research, efforts to determine the risk factors that predict nerve damage from elevated pressure should continue. With appropriately refined noninvasive instrumentation and other products of modern technology, it may be possible to learn about the mechanism of optic nerve damage in human glaucoma. Epidemiologic studies comparing persons whose eyes are not damaged by pressure with those whose eyes are highly sensitive to pressure may provide insight into the factors that are important in the genesis of the disease.

If evaluation of the status of the human optic disc is to be done quantitatively, present methods need to be developed further so that they can be used effectively in the average clinical office. This is an opportune time for careful clinical evaluation of automatic perimeters and development of improved methods of measurement of visual fields. Because these instruments are becoming popular, it is important to ensure that they are of acceptable accuracy and reliability, lest unsatisfactory instruments come into common use.

Finally, the time is right to explore a variety of psychophysical tests for evaluating various aspects of visual function and to determine if any might be useful in detecting glaucoma more promptly or be conducted more readily than standard perimetry. Interesting data on contrast sensitivity and some other aspects of visual function suggest that some quantitative psychophysical test may be simpler to perform and more sensitive than perimetry in signaling nerve damage in the early stages of glaucoma. It may be possible to devise new tests based on the growing body of knowledge about the several types of ganglion cells and their visual physiologic response, and to determine which types of cells are more susceptible to damage than others and why.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "The Optic Nerve," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or

no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

### *Program Base*

- Evaluate methods for measuring and recording changes in the optic disc, such as stereophotogrammetry.
- Conduct experimental studies of mechanisms of optic nerve damage in primary open-angle glaucoma and low tension glaucoma.
- Develop and evaluate new psychophysical tests for measuring optic nerve function and loss of visual function.
- Explore other methods for studying optic nerve damage.

### *Program Development Priorities*

- Pursue promising new leads to identify risk factors, or factors that are important in determining susceptibility of the optic nerve to the damaging effects of intraocular pressure.
- Develop innovative, noninvasive methods for studying the pathophysiologic mechanisms of nerve damage in humans due to glaucoma.
- Develop new psychophysical tests for measuring altered visual function in glaucoma and evaluate automatic perimetry.

## RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## PRIMARY OPEN-ANGLE GLAUCOMA

THE OPTIC NERVE

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Evaluate methods for measuring and recording changes in the optic disk, such as stereophotogrammetry. | 3 | −2 | 1 |
| B. Conduct experimental studies of mechanisms of optic nerve damage in primary open-angle and low tension glaucomas. | 6 | 2 | 8 |
| C. Develop and evaluate new psychophysical tests for measuring optic nerve function and loss of visual function. | 1 | 0 | 1 |
| D. Explore other methods for studying optic nerve damage. | 2 | 0 | 2 |
| **Program Development Priorities** | | | |
| A. Identify risk factors for nerve damage. | 2 | 1 | 3 |
| B. Develop new noninvasive methods for studying optic nerve damage and loss of visual function. | 2 | 2 | 4 |
| C. Develop new psychophysical tests for altered visual function and evaluate automatic perimetry. | 0 | 3 | 3 |
| **Subtotal Grants** | **16** | **6** | **22** |
| **(% of Program)** | **(18)** | **(17)** | **(18)** |
| **Total Estimated Cost** | **$1,771,000** | **$781,000** | **$2,552,000** |

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# OTHER GLAUCOMAS

# 5

# ANGLE-CLOSURE GLAUCOMA

## INTRODUCTION

*ANGLE-CLOSURE GLAUCOMA* accounts for 10–20 percent of adult glaucoma and for about 50 percent of all surgery for glaucoma in the United States. In angle-closure glaucoma, the iris comes into contact with the trabecular meshwork, preventing or slowing the filtration of aqueous humor and causing a rise in intraocular pressure. If this condition is recognized and treated promptly, the progression of the glaucoma and loss of vision can be prevented. Iridectomy, in which surgical excision of a tiny amount of iris tissue is performed, or laser iridotomy, in which a small hole is burned in the iris, are both very successful in restoring access of aqueous humor to the trabecular meshwork and a normal rate of filtration.

Angle-closure is generally related to anatomical peculiarities of the eye which are often inherited: the anterior chamber may be abnormally shallow, with an unusually narrow space between the iris and the trabecular meshwork. Certain factors may precipitate an attack of angle-closure glaucoma, among which are sudden pupil dilation, stress or trauma (Figure). In some patients, the onset of the disease is acute, with symptoms that include blurred vision, pain, and redness of the eye due to severely elevated intraocular pressure; in others, the onset is less dramatic. If not treated, angle-closure leads to adhesions between the iris and the meshwork which permanently seal off the filtration area. In a typical attack of angle-closure, miotic eyedrops can be used to widen the angle and restore normal aqueous flow and to keep the eye in a stable condition until surgery can be performed. Filtration through the angle becomes normal following successful surgery.

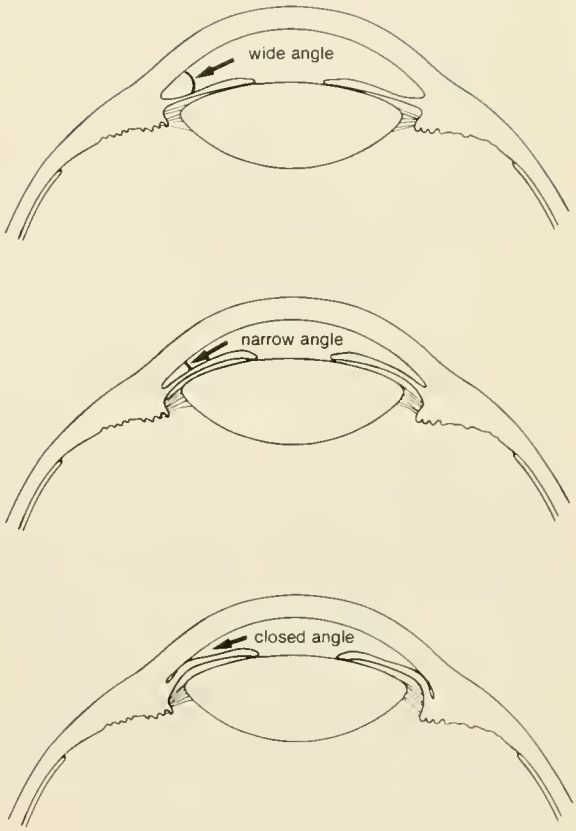


FIGURE. In an eye with a narrow angle, anterior movement of the iris can close the angle, obstruct outflow of aqueous humor, and cause pressure elevation.

There are several subtypes of angle-closure glaucoma. In primary angle-closure glaucoma, one subtype is caused by "pupillary block," in which the iris-trabecular contact occurs when the lens contacts the iris and obstructs the flow of aqueous humor from the posterior chamber to the anterior chamber; this, in turn, pushes the lens and iris

forward until the iris occludes the meshwork. In another condition, called "plateau iris," the anterior chamber does not appear to be abnormally shallow; in such instances, an anterior insertion of the iris into the ciliary body seems to be the important etiologic factor, although pupillary block may play a role. In "ciliary-block glaucoma," also known as "malignant glaucoma," misdirection of aqueous humor (or some kind of vitreous blockage) pushes the iris forward against the trabecular meshwork.

Secondary types of angle closure, which occur in eyes with normal anatomic configurations, are caused by conditions that lead to shallowing of the anterior chamber and closure of the angle. These conditions include lens subluxation, central retinal vein occlusion, scleritis, panretinal photocoagulation for retinal disease, and scleral buckling procedures for retinal detachment.

In some angle-closure patients, miotic eyedrops paradoxically cause the angles to close, either precipitating or worsening angle-closure glaucoma. It is not known whether these cases are a unique subtype of angle-closure glaucoma, nor what peculiar features cause this atypical response to treatment. Malignant glaucoma, too, is typically worsened with standard mitotic treatment, and uncharacteristically, may be relieved by cycloplegic agents, which worsen the common types of angle-closure glaucoma.

If it were known which types of eyes having anatomic abnormalities of the anterior chamber were at risk for angle-closure glaucoma, and what factors precipitate this condition, prophylactic surgery could be employed. However, only a few eyes with narrow angles will develop angle-closure glaucoma [1,2] and current methods which attempt to predict closure for diagnosis are not accurate. In fact, various provocative tests designed to induce angle closure are used less frequently now than in the past, because they all produce an unknown proportion of false positive results, an unacceptably high proportion of false negatives, or both.

# SUBPROGRAM OBJECTIVES

- To understand the anatomic abnormalities and the pathophysiologic basis of angle-closure glaucoma.
- To devise improved means for prognosis and diagnosis of angle-closure glaucoma.
- To improve clinical management of angle-closure glaucoma, evaluate various treatments, and define the indications for each.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

There has been very little formally supported research on angle-closure glaucoma. Most of what is known about the various types of angle closure and its management has resulted from the observations of astute clinicians. A National Eye Institute-supported collaborative study is exploring the natural history of primary angle-closure glaucoma in suspects (patients with narrow angles who have none of the symptoms of angle-closure) and the value of provocative testing in predicting the future status of their eyes. In FY 1981, the National Eye Institute supported three projects at a total cost of $155,000 in this subprogram.

# RECENT ACCOMPLISHMENTS

Among recent accomplishments in research on angle-closure glaucoma has been the gradual realization by experienced clinicians that not all cases of angle closure, perhaps not even the majority, are classical primary angle-closure glaucoma due to pupillary block. Rather, there appear to be several types of glaucoma caused by a mixture of mechanisms and accompanied by a spectrum of manifestations, each having differing natural histories.

A major technological advance is the use of laser energy to perform an iridotomy, [3–5] instead of the conventional surgical iridectomy. Initial results obtained by different investigators varied considerably, some being unable to achieve a satisfactory iridotomy using the types of lasers in common clinical use. An increasing number of clinicians now treat all of their angle-closure cases with the argon laser and claim a high rate of success with very few complications. Another laser technique used for certain cases involves shrinking the peripheral iris in a manner that prevents angle closure. [6]

An alpha-adrenergic receptor blocking drug, the miotic thymoxamine, [7] has been used in treating attacks of acute angle-closure glaucoma. It may be used to prevent inadvertent precipitation of angle-closure glaucoma in narrow-angled eyes after dilation of the pupil for retinal examination, and perhaps it can be used for chronic treatment in certain types of angle closure.

Mapstone [8] has analyzed some of the theoretical physical factors involved in pupillary block; this thoughtful type of assessment should be applied to all the mechanical factors involved. Spaeth [9] has initiated a classification of angle configuration that

ultimately may be related to the type of glaucoma and its natural history. The increasing use of indentation gonioscopy[10,11] to judge the amount of synechiae (adhesions between the iris and the trabecular meshwork) present, to decide whether iridectomy or filtration surgery is required, has led to a new therapeutic approach[12] for breaking angle-closure attacks mechanically, often avoiding the need for systemic administration of osmotic agents.

# RESEARCH NEEDS AND OPPORTUNITIES

The various anatomic abnormalities and mechanisms involved in the etiology of angle closure need to be defined and subtypes of the disease should be described as separate entities. An understanding of the different factors that may predominate in various subtypes of angle-closure glaucoma and the ability to differentiate among them in particular instances should enhance the clincian's ability to choose optimal treatments for individual patients. It would be especially helpful to develop criteria for recognizing reliably the instances in which pupillary block is the primary mechanism of angle closure (for example, by quantifying the degree of pupillary block) and for distinguishing cases in which there is a ciliary block or vitreous pressure in malignant glaucoma. Other conditions that may precipitate angle closure are related to ciliary body swelling, lens enlargement, or lens movement. In particular, risk factors that predispose only some narrow-angled eyes to angle closure need to be determined so that appropriate treatment of only those eyes can be instituted or devised. The availability of improved methods of biometric measurement should stimulate interest in studying factors not yet studied quantitatively (for example, iris thickness, iris color, and location of iris insertion). Careful biometric categorization, including correlations with the natural course of the disease(s) and responses to provocative testing, may suggest new therapeutic approaches. Data from new types of provocative tests based on measurable factors (other than angle-closure and pressure elevation) may correlate with the natural course of angle-closure glaucoma.

Meanwhile, clinical trials can be used to determine the best choices for therapy in certain well-defined clinical situations by answering such questions as: Are openings in the iris produced more effectively and safely by surgery than with the laser? Are there types of cases in which chronic miotic treatment would adequately prevent angle-closure, that is, those in which the angle is deepened markedly by pilocarpine? Should iridectomy or laser iridotomy be used in addition to chronic miotic therapy to treat plateau iris? Can the stage of the disease be identified prior to surgery in instances when filtration surgery rather than iridectomy is necessary? Is it helpful to break synechiae at any stage of their formation by chamber deepening or enzymatic means? Given the risk of ocular damage from a single attack of angle-closure compared with the risk of complications from surgery (iridectomy) and the partially preventive role of chronic miotic therapy, should the initial therapy be chronic miotic treatment, and should chronic miotic treatment be used before laser iridotomy? Is angle-closure secondary to vein occlusion or scleral buckling better treated with miotics, cycloplegics, or surgery? Is thymoxamine a more effective miotic agent than pilocarpine for the treatment of acute angle-closure glaucoma? It has been proposed that thymoxamine, a pure alpha-adrenergic receptor blocker which only dilates the pupil, be used to differentiate angle-closure glaucoma from possible open-angle glaucoma with a narrow angle. It is not known if the apparent open-angle component of such cases is actually an intermittently closed angle accompanied by damage to the trabecular meshwork.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Angle-Closure Glaucoma," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

### *Program Base*

- Develop reliable predictive tests and diagnostic criteria for potential angle-closure.
- Improve and evaluate therapy for angle-closure glaucoma.

### *Program Development Priorities*

- Describe the pathogenesis of angle-closure glaucoma, subtypes of the disease, and develop or verify tests to identify subtypes of angle-closure glaucoma.
- Evaluate the efficacy of initial therapy with miotic drugs in preventing angle-closure in eyes at risk, and determine if any benefit of long-term treatment could be predicted from early drug effects on anterior chamber configuration.

## RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## OTHER GLAUCOMAS

ANGLE-CLOSURE GLAUCOMA

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Develop predictive and diagnostic criteria for angle closure. | 2* | 0 | 2 |
| B. Improve and evaluate therapy for angle-closure glaucoma. | 1 | 0 | 1 |
| **Program Development Priorities** | | | |
| A. Describe the pathogenesis of angle-closure glaucoma and subtypes of the disease. | 0 | 2 | 2 |
| B. Evaluate the efficacy of initial therapy with miotic drugs in preventing angle-closure in eyes at risk, and determine if any benefit of long-term treatment could be predicted from early drug effects on anterior chamber configuration. | 0 | 1 | 1 |
| **Subtotal Grants** | **3** | **3** | **6** |
| **(% of Program)** | **(3)** | **(9)** | **(5)** |
| **Total Estimated Cost** | **$155,000** | **$541,000** | **$696,000** |

***Collaborative study: Natural History of Angle-Closure Glaucoma Suspects.**

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# 6

# DEVELOPMENTAL, CONGENITAL, AND INFANTILE GLAUCOMAS

## INTRODUCTION

*GLAUCOMA IN CHILDREN* is a severe disease, and its visual effects are often devastating, frequently condemning the child to a lifetime of blindness. Although developmental glaucoma is uncommon, it accounts for 5 percent of legal blindness in children. Childhood glaucomas are caused by many different mechanisms that impair outflow of aqueous humor. Some are primary, due to maldevelopments of the aqueous humor outflow channels; others are secondary, associated with and often caused by other ocular or systemic diseases.

The nomenclature of glaucoma in children is imprecise, is not standardized, and may not reflect the underlying pathology. The terms "congenital," "infantile," and "developmental" are often applied interchangeably, but actually each has a slightly different meaning. Congenital glaucoma is clinically manifest at birth and is nearly always caused by a developmental anomaly. Infantile glaucoma is defined as beginning before the age of one year and thus includes congenital glaucomas and postnatal glaucomas. Although infantile glaucoma is usually due to a developmental anomaly, some postnatal types are acquired, for example, following injury, infection, surgery for cataract, or the use of corticosteroids. Developmental glaucoma includes those that result from abnormal development of the aqueous humor outflow channels, regardless of the time of onset, and may be primary or secondary. Primary developmental glaucoma probably includes several disorders, each caused by a slightly different type of chamber angle developmental anomaly.

Classification of the developmental glaucomas has been hindered because the terms used to describe the appearance of the chamber angle in the living eye, as observed with a gonioscope, vary from clinic to clinic. In part, this reflects insufficient information for relating gonioscopic appearances of the anterior chamber angle to corresponding histopathologic abnormalities. The lack of an accepted worldwide nomenclature for these types of glaucoma and means of describing them impedes not only scientific communication but studies of their prevalence, natural history, and response to therapy.

The eye of a child, compared with that of an adult, is particularly susceptible to damage from high intraocular pressure. Children often develop optic atrophy, disc cupping, and profound visual loss at levels of intraocular pressure that, although elevated, would not damage most adult optic nerve heads. Furthermore, the cornea and sclera of the young eye, unlike those of the adult eye, stretch when intraocular pressure is high. Stretching of the cornea often causes tears in Descemet's membrane (an acellular membrane that lines the back of the cornea) and corneal edema, with later healing which leaves semi-opaque scars, astigmatism, and optical impairment of vision. Stretching of the sclera causes the entire eye to enlarge, a condition known as buphthalmos, and in some eyes leads to high myopia, amblyopia, lens dislocation, unusual susceptibility to subsequent injury, and disfigurement.

In children, loss of vision from glaucoma frequently can be prevented, but only if the disease is detected early and treated aggressively. In infants severely affected with glaucoma, optic atrophy and buphthalmos may be present at birth. Even if the optic nerve has not been completely damaged before birth, severe congenital glaucoma is difficult to treat successfully and has a worse prognosis than

glaucomas that begin later in childhood. The diagnosis and treatment of less severe infantile glaucoma are often delayed because primary care physicians, who rarely encounter this disease, may be unfamiliar with its signs and symptoms. Because medical treatment of infantile glaucoma is relatively ineffective, control of the disease, once it is correctly diagnosed, may require multiple hospitalizations, examinations under anesthesia, and ocular surgical procedures. Surgical treatment is more successful in primary infantile glaucoma than it is in many kinds of secondary infantile glaucoma. Even if treatment is successful in lowering intraocular pressure and preventing progressive optic nerve damage, secondary effects, such as amblyopia or corneal scarring and edema, may continue to impair vision and require additional treatment. Psychologic, sociologic, and rehabilitative help for both visually handicapped children and their parents is important. Thus, childhood glaucoma presents a difficult problem, whose severity and impact are out of proportion to the relatively low incidence of the disease.

Research progress in improving diagnosis and therapy of the childhood glaucomas has been discouragingly slow. Because infantile glaucoma is uncommon, few research centers have been able to accumulate enough patients for meaningful clinical research. Clinical studies also have been impeded by the difficulty of examining uncooperative infants and young children. General anesthesia, which is often necessary for a complete examination, alters intraocular pressure and cannot be repeated frequently with safety. However, studies of normal anterior chamber angle development in man and primates are shedding light on how faulty angle development might occur. Information from physiologic and pharmacologic research on control of intraocular pressure in adults is also applicable to children. Other broad research areas, such as child health and congenital and developmental disorders in general, relate to the study of childhood glaucomas.

# SUBPROGRAM OBJECTIVES

- To broaden knowledge of the normal and pathologic development of the anterior chamber angle and aqueous humor drainage channels of man and primates and to differentiate the various types of glaucoma in young children.
- To improve techniques for measuring intraocular pressure and aqueous humor dynamics, examining the anterior chamber angle, and evaluating visual function in children.
- To evaluate medical and surgical therapies for treating infants and children with glaucoma.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981, the National Eye Institute supported two projects at a total cost of $137,000, that dealt directly with developmental glaucoma. One study of the classification, etiology, and therapy of human congenital glaucoma had as its goals establishment of a uniform clinical terminology and an assessment of the long-term results of therapy in each type of developmental glaucoma. The other studied congenital buphthalmos in the rabbit. A number of other NEI-supported studies, classified in other Glaucoma subprograms, included projects relevant to developmental glaucoma, such as electron microscopic examination of trabeculectomy specimens from cases of developmental glaucoma, studies of mammalian aqueous humor outflow channels, and anatomic examinations and perfusion experiments with eyes from normal fetal and neonatal monkeys. Information on the development of the normal primate chamber angle will increase understanding of abnormalities in human developmental glaucoma.

Research currently supported by the National Eye Institute and other funding organizations does not include studies of better ways to evaluate intraocular pressure and visual function in children with glaucoma, nor does it include controlled clinical trials of medical and surgical therapies for childhood glaucoma.

# RECENT ACCOMPLISHMENTS

Children who have suffered optic nerve damage from glaucoma in infancy later have cupping of the optic disc and visual field abnormalities similar to those found in adult glaucoma.[1] This implies that the pathogenetic mechanism for optic nerve damage is the same in all age groups and that results of studies of optic nerve damage in adult glaucoma are applicable to childhood glaucoma.

Recent studies in birds have indicated that the tissues lining the anterior chamber angle originate during embryonic development from the neural crest rather than the mesoderm, as formerly thought.[2–4] This observation, if it proves valid for mammals, should stimulate new research into the origin and normal development of chamber angle

tissue, which in turn may provide new insights into the pathogenesis of some developmental glaucomas.

Glaucoma in the Sturge-Weber syndrome, a congenital vascular malformation of the skin and brain as well as the eye, has been shown to be caused by high episcleral venous pressure resulting from arteriovenous shunting in episcleral hemangiomas.[5] This observation explains why conventional surgery often fails and may open the door to more successful management of this secondary developmental glaucoma.

Aniridia, or congenital absence of most of the iris, is frequently associated with secondary developmental glaucoma. Most aniridia is dominantly inherited, but some cases are sporadic. Many of the sporadic cases have other systemic abnormalities including Wilms' tumor of the kidney. The aniridia-Wilms' tumor syndrome recently was found to be caused by deletion of the short arm of chromosome 11.[6]

Open-angle glaucoma has been found to occur in many patients who years earlier had surgery for congenital cataracts,[7] although the cause of this secondary glaucoma is still unclear.

# RESEARCH NEEDS AND OPPORTUNITIES

Present information about the normal development of the primate anterior chamber angle is confusing because different investigators in this field, using mainly light microscopic examination of a limited number of specimens, have reached differing conclusions. The embryonic development of the normal chamber angle needs to be reexamined using newer techniques such as scanning electron microscopy, injection molds, and cell markers. There is also a need to alter chamber angle development experimentally in animal fetuses and correlate the histologic appearance of the induced developmental abnormalities with those found in human developmental glaucoma.

Accurate measurement of intraocular pressure, which is necessary for diagnosis and for monitoring the efficacy of therapy, is often difficult in children because of lack of cooperation. Although anesthesia and sedative drugs allow pressure to be measured accurately, currently used agents also alter pressure dramatically and unpredictably. New studies of the effects of various anesthetic agents on intraocular pressure should be conducted. These studies should include rigid standardization of the depth of anesthesia and should use applanation tonometry for pressure measurement while the patient is lying supine. New general anesthetic agents, especially those that have little effect on the autonomic nervous system, merit particular attention. Alternatively, there is a need for the development of noncontact tonometric techniques suitable for measurement of intraocular pressure in awake children.

Lack of common terminology to describe the results of gonioscopic observations of the infantile chamber angle, both normal and abnormal, has hampered the development of a widely-accepted classification of developmental primary glaucoma. Standardized methods of measuring and evaluating the anterior chamber angle, including means of stereoscopic angle photography, must be developed so that a universally accepted descriptive nomenclature can be developed. Although the optic nerve head of a child can be evaluated for structural damage by ophthalmoscopy, visual function is often difficult to assess. Improved objective methods should be devised for evaluating damage to vision due to glaucoma in children. These methods might involve measurement of visually evoked electrical cortical responses to contrast gratings or to ophthalmoscopically controlled retinal light stimulation.

Current medical therapy for developmental glaucoma is disappointing. Development of new drugs and delivery systems that are applicable to treating children effectively is necessary. Any new treatments should be tested in carefully controlled clinical trials.

Improved means should be found for alerting primary care physicians to the earliest signs of infant eye abnormalities and the need for immediate referral of suspected cases of glaucoma to ophthalmologists.

The successes of goniotomy and trabeculotomy in infants and children with glaucoma are often dramatic, even though the mechanisms by which these operations improve outflow are unclear, and no prospective randomized study has compared the efficacy and safety of these two widely used procedures. Clinical observations suggest that glaucoma arising in infancy responds well to goniotomy or trabeculotomy but that severe glaucoma either present at birth or developing in older children responds less well. Thus, the efficacy of surgical approaches to treatment of each class of glaucoma must be evaluated separately. For example, preventive surgery may be the best approach for some types of aniridia;[8] this needs to be evaluated in a clinical trial. Better understanding of the pathogenesis of the various developmental glaucomas is necessary before the varied responses to therapy can be explained.

Because glaucoma in children occurs infrequently, research should be facilitated by the development of special regional centers, cooperative multicenter studies, and a national registry for the study of surgical or postmortem specimens.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Developmental, Congenital, and Infantile Glaucoma," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

### *Program Base*

- Develop a classification system for childhood glaucoma.
- Conduct experimental studies in animals to determine causes of developmental and congenital glaucomas, improve means of measuring intraocular presure and visual function, and develop improved anesthesia for children.

### *Program Development Priorities*

- Establish a national registry for the exchange and study of surgical and postmortem specimens from children with developmental, congenital, and infantile glaucoma and correlate histological observations with standard clinical descriptions and natural history observations.
- Develop cooperative programs to improve understanding of the natural history and the treatment of glaucoma in children.

# RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## OTHER GLAUCOMAS

DEVELOPMENTAL, CONGENITAL, AND INFANTILE GLAUCOMAS

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Develop a classification system for childhood glaucoma. | 1 | 0 | 1 |
| B. Conduct experimental studies in animals. | 1 | 0 | 1 |
| **Program Development Priorities** | | | |
| A. Establish a national registry of surgical and postmortem specimens from children with developmental, congenital, and infantile glaucoma. | 0 | 1 | 1 |
| B. Develop cooperative programs to improve understanding of natural history and treatment of glaucoma in children. | 0 | 2 | 2 |
| **Subtotal Grants** | **2** | **3** | **5** |
| **(% of Program)** | **(2)** | **(9)** | **(4)** |
| **Total Estimated Cost** | **$137,000** | **$443,000** | **$580,000** |

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# 7

# SECONDARY GLAUCOMAS

## INTRODUCTION

*A VARIETY OF OCULAR* diseases and conditions, such as vascular disease, inflammation, injury, or tumors, may impede the outflow of aqueous humor and produce elevated intraocular pressure. The glaucomas that result are "secondary glaucomas." Depending upon their origin, some of these types of glaucoma are unresponsive to treatment and difficult to control; therefore, they more often lead to blindness than do the primary glaucomas.

Neovascular glaucoma is a particularly disastrous type of glaucoma which usually occurs secondary to retinal vascular diseases. In this condition, abnormal new fibrovascular tissue proliferates on the surface of and within the iris and ciliary body and grows over the surface of the trabecular meshwork. Initially, this fibrovascular overgrowth ("rubeosis") obstructs aqueous humor outflow and causes increased intraocular pressure. At a later stage of the disease, the fibrovascular membrane contracts and pulls the iris against the meshwork, causing formation of irreversible peripheral anterior synechiae and marked elevation of intraocular pressure. Conventional medical therapy and filtering surgery are almost always ineffective in treating neovascular glaucoma; and more radical treatments aimed at destroying the ciliary body tissue, to diminish production of aqueous humor, also are fraught with complications. Many, if not most, of such eyes eventually lose all vision, either from the neovascular glaucoma itself, the associated ocular disease, or the destructive treatments. Often, the only treatment available is to relieve the excruciating pain associated with the markedly elevated intraocular pressure and the accompanying inflammation or, failing that, remove the entire eye.

Most frequently, in neovascular glaucoma, the underlying condition is related to retinal ischemia, which may be associated with proliferative diabetic retinopathy, central retinal vascular occlusions, a variety of other retinal microvascular disorders, or carotid insufficiency. Occasionally, longstanding uveitis, retinal detachment, or anterior or posterior segment tumors can lead to neovascular glaucoma. In diabetics, at least, the best treatment for neovascular glaucoma appears to be to prevent it by early treatment of the proliferating retinal vessels by laser photocoagulation.[1,2]

As the treatment of diabetes has improved, more patients live long enough to develop the posterior ocular complications that lead to neovascular glaucoma. Also, some of the treatments for posterior segment diabetic disease (for example, vitrectomy) may lead to or exacerbate anterior segment neovascularization and neovascular glaucoma. Furthermore, the incidence of diabetes may be increasing, because diabetics who in the past would have died at an early age now live into their reproductive years and may pass on susceptibility to the disease to their offspring. Thus, the incidence and prevalence of neovascular glaucoma are steadily increasing.

Other types of secondary glaucoma include those caused by injury, inflammation, ocular surgery, tumor, hemorrhage, diseases that raise episcleral venous pressure, disorders of the lens, pigmentary dispersion, and degenerative conditions of unknown etiology. Included among the traumatic glaucomas are chronic angle-closure glaucoma due to formation of synechiae after a penetrating injury, high intraocular pressure due to hyphema, acute and chronic open-angle glaucoma caused by contusion and angle recession, and siderotic glaucoma due to a retained iron foreign body. Inflammatory glaucomas include angle-closure glaucoma due to posterior or anterior synechiae, glaucomatocyclitic crisis, open-angle glaucoma caused by acute or chronic iridocyclitis, Fuchs' heterochromic cyclitis, and glaucoma

secondary to scleritis or interstitial keratitis. Glaucoma may follow surgery for cataract, corneal disease, or retinal detachment. Retinoblastoma and uveal melanoma may cause glaucoma by several pathogenetic mechanisms.

Vitreous hemorrhage may cause a chronic open-angle glaucoma if cellular debris released from the hemorrhage obstructs aqueous humor outflow. Intracranial arteriovenous fistulas and the Sturge-Weber syndrome cause glaucoma by raising episcleral venous pressure. Denatured lens protein, leaking through the capsule of a hypermature cataract, elicits a macrophagic cellular reaction; the macrophages and the high molecular weight proteins themselves obstruct outflow and produce open-angle "phacolytic" glaucoma.[3] Dispersion of pigment from the back of the iris (especially in myopic males) may lead to "pigmentary" glaucoma. Dislocated or spherophakic lenses and intumescent cataracts may block aqueous humor flow through the pupil and cause angle-closure glaucoma. Essential iris atrophy, Chandler's syndrome, and iris nevus syndrome are examples of degenerative disorders that cause glaucoma by formation of peripheral anterior synechiae. Exfoliation syndrome is a degenerative disorder in which material containing glycosaminoglycans is secreted into the eye and blocks aqueous humor outflow.

Each type of secondary glaucoma has a unique pathogenesis, characteristic clinical signs, and an individual response to therapy. Thus, each must be studied separately. Although the secondary glaucomas as a group occur frequently and constitute an important cause of blindness due to glaucoma, individual types may be rare. A single medical center may have difficulty in accumulating enough patients in any one category for meaningful clinical research. However, research into some types of secondary glaucoma could be facilitated by the relative ease with which animal models might be produced; posttraumatic glaucoma, inflammatory glaucoma, postsurgical glaucoma, and glaucoma secondary to intraocular hemorrhage are especially amenable to induction and study in animal models. Unfortunately, no suitable animal model for study of neovascular glaucoma has yet been produced.

Research on secondary glaucoma relates directly to many other areas of vision research, especially studies of: retinal diseases (neovascular glaucoma, glaucoma secondary to or associated with retinal detachment, and glaucoma after scleral buckling operation); corneal diseases (essential iris atrophy, Chandler's syndrome, posterior polymorphous dystrophy, and glaucoma induced by keratoplasty); uveitis (the various inflammatory glaucomas listed above); and lens diseases (phacolytic glaucoma, phacomorphic glaucoma, and glaucomas associated with lens dislocation). In addition, research on secondary glaucoma relates to other areas of biomedicine such as diabetes and oncology.

# SUBPROGRAM OBJECTIVES

- To improve descriptions of the natural history of each type of secondary glaucoma.
- To understand the pathogenetic mechanisms of the various secondary glaucomas.
- To design and test specific treatments for each type of secondary glaucoma.
- To develop clinically relevant animal models for specific types of secondary glaucoma.

# OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981, the National Eye Institute supported 11 projects at a total cost of $836,000, in which disease mechanisms relevant to secondary glaucomas were studied. Research efforts directed to secondary glaucomas involved studies on topics related to: ocular inflammation in the anterior chamber and cellular products of the inflammatory response; the roles of autacoids in the anterior chamber; pigment dispersion syndrome; and exfoliation syndrome.

# RECENT ACCOMPLISHMENTS

The apparent etiologic association of neovascular glaucoma with retinal ischemia, which also may lead to retinal neovascularization, has led to a search for pathophysiological mechanisms or factors by which ischemia might produce neovascularization. It has led also to a search for new treatments such as panretinal photocoagulation, designed to reduce the neovascular complication of retinal ischemia. Some investigators have isolated from the vitreous of involved eyes a putative "vasogenic factor" which may be produced by the ischemic retina and diffuse through the vitreous to produce the iris disease and glaucoma. Others have sought to induce ocular neovascularization in animals with iatrogenic diabetes,[4] central retinal vascular occlusion,[5] immunogenic uveitis,[6,7] or local irradiation,[8]

none of which has produced a condition comparable with that in the human. Some investigators have studied ocular neovascularization induced by tumors, leukocytes, inflammation, or chemicals[9–19] and searched for the means to inhibit it.[20–22] The latter studies eventually may shed light on factors involved in iris and chamber angle neovascularization processes.

Two studies have suggested that eyes treated with panretinal photocoagulation at an appropriate stage of diabetic retinopathy are less apt to develop anterior segment neovascularization and neovascular glaucoma than untreated control eyes.[1,2] Many investigators have the strong clinical impression that panretinal photocoagulation also is beneficial in the later stages of the disease by causing regression of established anterior and posterior segment neovascularization. Although this procedure would not open an angle that is completely sealed with peripheral anterior synechiae, it may help to normalize intraocular pressure in an eye with a partly open angle and make it easier to control intraocular pressure medically or reduce the likelihood of severe hemorrhage after subsequent surgery. One study has suggested that direct argon laser photocoagulation of new vessels in the anterior chamber angle may arrest early neovascular glaucoma, especially when combined with panretinal photocoagulation.[23] However, experience with this technique has not satisfied other investigators. Modified trabeculectomy[24] and implantation of the Krupin-Denver or Molteno valves[25,26] have produced promising short-term results in a small series of carefully selected cases of neovascular glaucoma; these methods need to be validated in larger studies.

Secondary open-angle glaucoma may develop from degeneration of red blood cells in a large vitreous or anterior chamber hemorrhage. Previously, this secondary glaucoma was thought to be caused by hemoglobin-laden macrophages plugging the aqueous drainage channels ("hemolytic glaucoma"). However, recent studies have demonstrated that eyes with a degenerating intraocular hemorrhage and glaucoma contain a large number of erythroclasts (ghost cells, red blood cells that have lost their hemoglobin) which are nonpliable and do not deform to squeeze through the trabecular meshwork as do normal red blood cells.[27,28] Instead, they occlude the meshwork channels and produce "ghost cell" or "erythroclastic" glaucoma. What remains uncertain is whether the ghost cell mechanism is the sole reason for the glaucoma or if macrophages also are responsible for obstructing the meshwork.

Phacolytic glaucoma had been thought to result from a blockage of the meshwork by macrophages laden with lens proteins that leak from a cataractous lens. Recent data have shown that aggregated high molecular weight lens proteins themselves can obstruct outflow.[3,29]

Essential iris atrophy, Chandler's syndrome, the Cogan-Reese iris nevus syndrome, and posterior polymorphous corneal dystrophy are four diseases that cause secondary glaucoma. Each is characterized by corneal endothelial dystrophy, progressive peripheral anterior synechiae, obstructed outflow of aqueous humor, and varying degrees of iris degeneration. The first three disorders have been shown to share a common histopathologic abnormality, overgrowth of the trabecular meshwork and iris by corneal endothelial cells and Descemet's membrane,[30–32] and some authorities now consider them variants of a single "iridocorneal endothelial syndrome."[33,34] In posterior polymorphous dystrophy, an overgrowth of corneal endothelium and Descemet's membrane is also seen, but the endothelial cells have many ultrastructural features of epithelial cells.[35] This histologic difference, together with clinical differences, suggests that posterior polymorphous dystrophy is separate from the other iridocorneal endothelial diseases.

Ciliary body swelling recently has been reemphasized as a rare cause of angle-closure glaucoma, particularly after scleral buckling operations[36] and panretinal photocoagulation.[37]

Sickle cell disease places black patients with hyphema in double jeopardy.[38] First, because sickled red blood cells are rigid and cannot pass through the trabecular drainage channels, they obstruct aqueous humor outflow and produce glaucoma. Second, the optic nerve of patients with sickle cell disease is unusually susceptible to ischemia when intraocular pressure is high.

A longstanding mystery is how a tear in the ciliary body induced by an ocular contusion can lead years later to angle-recession glaucoma. Recent studies have shown that an ocular contusion severe enough to cause an angle recession frequently also tears the trabecular meshwork.[39] The trabecular tears are visible by gonioscopy but soon heal, leaving nearly invisible scars. The trabecular damage, not the angle recession, may be the cause of the glaucoma.

High prostaglandin levels have been detected in the aqueous humor of patients with glaucomatocyclitic crisis. Polyphloretin phosphate, a prostaglandin antagonist, causes a rapid lowering of intraocular pressure in such patients,[40] implying that prostaglandins play a causative role in at least this type of secondary inflammatory glaucoma. The abnormally high concentration of aqueous humor protein observed in ocular inflammation may play a role in glaucoma secondary to inflammation. Studies in perfused enucleated eyes have demonstrated that moderate concentrations of serum proteins in the aqueous humor increase outflow resistance.[41]

Electron microscopic studies of eyes with pseudoexfoliation have revealed that the abnormal material deposited inside the eye also is found around conjunctival and orbital vessels.[42,43] This material, which has a characteristic ultrastructural appearance, has been found in the conjunctiva of uninvolved fellow eyes[44] but nowhere else in the body. Within the eye, the pseudoexfoliation material is found between the lens epithelium and capsule,[45,46] in the basement membrane of the iris and ciliary epithelium,[47,48] around iris vessels,[48,49] on the surface of the lens capsule, and in the trabecular meshwork. This abnormal material resembles amyloid, and histochemical studies suggest that it is a glycosaminoglycan.[50]

Finally, a mechanism has been proposed to explain why pigment is lost from the back of the iris in pigmentary glaucoma.[51] Strong evidence suggests that an anatomic relationship in certain eyes, perhaps especially in myopic eyes, allows contact between the zonular fibers and the iris, which causes pigment to rub off as the pupil contracts and expands.

# RESEARCH NEEDS AND OPPORTUNITIES

Apart from the fact that posterior segment ischemic diseases seem to predispose eyes to both posterior and anterior segment neovascularization, knowledge of the pathophysiology of ocular neovascularization is sparse. A first step in improving understanding of this condition is to define carefully the epidemiology and natural history of anterior segment neovascularization and neovascular glaucoma. Fluorescein angiography of the retina and iris may be of predictive value and should be studied further, perhaps combined with fluorophotometry of the vitreous.

An animal model for neovascular glaucoma is needed. With such a model, use of the powerful biochemical, physiological, pharmacological, ultrastructural, tissue culture, and cell biological techniques currently available might help to unravel all the mysteries of the neovascularization process and lead to effective preventive and therapeutic measures. Perhaps an appropriate ocular model could be developed in an existing model for one of the predisposing human diseases; for example, iatrogenically diabetic rats,[52] dogs,[4] and monkeys[4] all develop some of the ocular attributes of human diabetic retinopathy, although to date none of these species has developed the full-blown sequence of proliferative retinopathy, subsequent iris neovascularization, and glaucoma that occurs in man. In such a model the specific mediator(s) of the neovascularization process should be sought: the elusive, presumably diffusible, angiogenic or vasoproliferative factor.[53] It is vital to attract basic scientists with the appropriate skills to collaborate in this work.

Basic research on putative neovascularization factors in nonocular tissues may be relevant to the problems of neovascular glaucoma. The mechanism by which cells (tumor cells, macrophages, or normal tissue cells) produce angiogenic factors under conditions of low oxygen tension needs to be studied.

While pursuing these difficult and probably distant goals, simultaneous efforts should be directed to improving current treatment of established and incipient anterior segment neovascularization and neovascular glaucoma. Because of the relatively poor long-term results of current medical therapy, attention should be focused on clinical studies of new drugs for neovascular glaucoma as they become available. The efficacy of panretinal photocoagulation and goniophotocoagulation in preventing and treating rubeosis and glaucoma should be studied more systematically than in the past, and the optimal uses of these procedures should be defined, taking into account the findings obtained from the epidemiological and natural history studies.

Controlled clinical trials of the modified trabeculectomy and valve insertion procedures also are needed, not only to evaluate the surgery itself but also to determine its appropriate timing and optimal pre- and postoperative management strategies. Such clinical trials should be conducted as collaborations among investigators at centers seeing large numbers of patients and by physicians with significant interest and experience in dealing with rubeosis and neovascular glaucoma.

Controlled studies are needed to evaluate measures for preventing rebleeding in eyes with hyphema due to a contusion injury. Animal models should be developed for use in clarifying the pathogenetic mechanisms responsible for the high intraocular pressure that often accompanies hyphema. These models would also permit the testing of various treatments.

The pathogenetic mechanism of late glaucoma associated with traumatic angle recession should be clarified as well. Investigators need a way to predict which contused eyes are at risk of developing late glaucoma. In patients with unilateral angle recession glaucoma, the fellow eye often is unusually sensitive to the pressure-raising effect of topical glucocorticoids.[54,55] It is not known if corticosteroid sensitivity is a risk factor for angle-recession glaucoma, nor is it known if testing for sensitivity to corticosteroids would have predictive value in assessing the risk to fellow eyes of patients with hyphema.

The roles of prostaglandins, substance P, histamine, and other inflammatory mediators in the pathogenesis of inflammatory glaucoma need clarifi-

cation, and the effectiveness of specific anti-inflammatory drugs should be determined. Indeed, all studies relating to the etiologic and pathogenetic mechanisms of inflammation and the ocular immune responses, and specifically uveal inflammation, should be relevant to the understanding and treatment of glaucoma secondary to uveitis.

Transitory high intraocular pressure frequently occurs in the first few days after cataract surgery. The causes of this pressure elevation should be defined so that specific remedies or preventive measures can be devised. Also, the possible risks to vision imposed by high intraocular pressure in the postoperative period should be clarified. [56]

A common histopathologic feature of a number of secondary glaucomas is abnormal growth of the corneal endothelium and Descemet's membrane over the trabecular meshwork. More information is needed about the control mechanisms that normally prevent this endothelial growth and the stimuli for its occurrence in such diverse pathologic conditions as essential iris atrophy, Chandler's syndrome, iris nevus syndrome, posterior polymorphous corneal dystrophy, and angle recession. The possible relationship, if any, between Fuchs' corneal dystrophy and glaucoma needs to be reexamined.

The origin and nature of the abnormal material formed in eyes with pseudoexfoliation should be defined precisely, and the cellular and biochemical events in its formation identified. Epidemiologic, clinical, and pathologic studies may explain why only some eyes with pseudoexfoliation develop glaucoma.

There are many other secondary glaucomas, each of which requires unique basic laboratory and clinical studies. Among these are pigment dispersion glaucoma, glaucoma associated with retinal detachment, epithelial invasion, hemolytic glaucoma, and phacolytic glaucoma. Animal models of the various types of secondary glaucoma should be developed and studied critically, as should spontaneous glaucoma in animals that resemble any type of human secondary glaucoma.

# RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Secondary Glaucomas," the Panel has made the following recommendations concerning research in this area over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

## *Program Base*

- Study the pathogenetic mechanisms of inflammatory glaucoma.
- Study the pathogenetic mechanisms of low frequency glaucomas and test therapies.

## *Program Development Priorities*

- Study the natural history of neovascular glaucoma.
- Study the natural history of low frequency glaucoma.
- Study the pathogenetic mechanisms of neovascular glaucoma.
- Test treatments for neovascular glaucoma.
- Test treatments for inflammatory glaucoma.

# RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

# RESOURCE TABLE

## OTHER GLAUCOMAS

SECONDARY GLAUCOMAS

| | No. of Grants FY 1981 | Panel Recommendation FY 83 | |
|---|---|---|---|
| | | Add. Grants | Total Grants |
| **Program Base** | | | |
| A. Study the pathogenetic mechanisms of inflammatory glaucoma. | 7 | −4 | 3 |
| B. Study the pathogenetic mechanisms of low frequency glaucomas and test therapies. | 1 | 0 | 1 |
| **Program Development Priorities** | | | |
| A. Study the natural history of neovascular glaucoma. | 1 | 1 | 2 |
| B. Study the natural history of low frequency glaucoma. | 1 | 1 | 2 |
| C. Study the pathogenetic mechanisms of neovascular glaucoma. | 1 | 2 | 3 |
| D. Test treatments for neovascular glaucoma. | 0 | 1 | 1 |
| E. Test treatments for inflammatory glaucoma. | 0 | 2 | 2 |
| **Subtotal Grants** | **11** | **3** | **14** |
| **(% of Program)** | **(12)** | **(9)** | **(11)** |
| **Total Estimated Cost** | **$836,000** | **$788,000** | **$1,624,000** |

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